The effect of DAFNE education, continuous subcutaneous insulin infusion, or both in a population with type 1 diabetes in Scotland

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The effect of DAFNE education, CSII, or both in a population with Type 1 diabetes in Scotland

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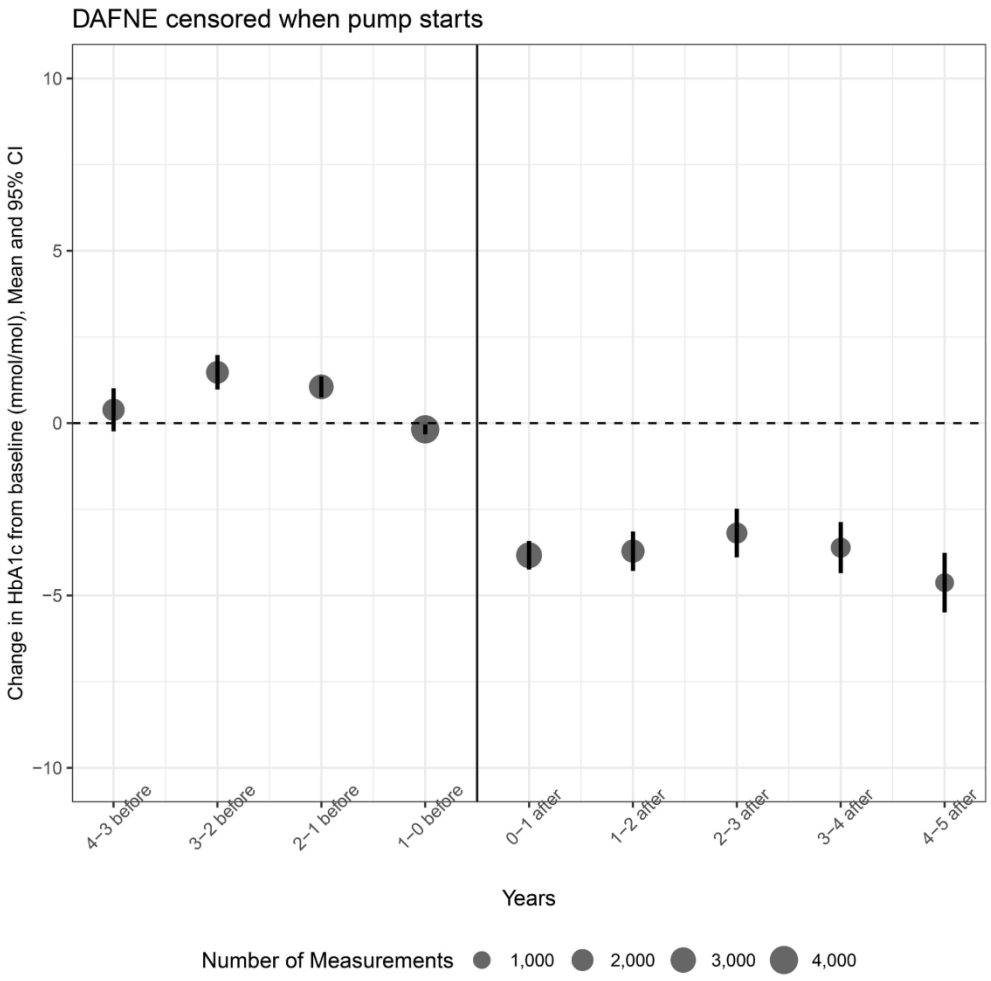

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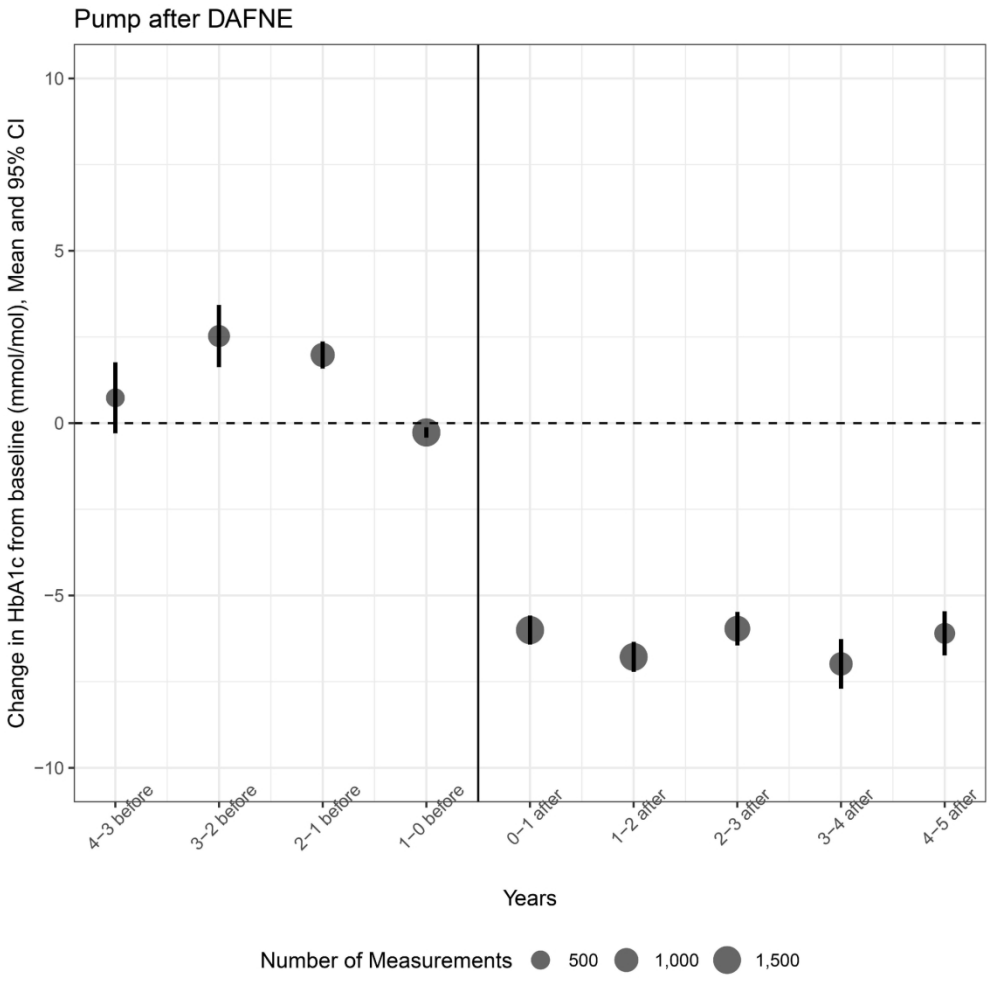

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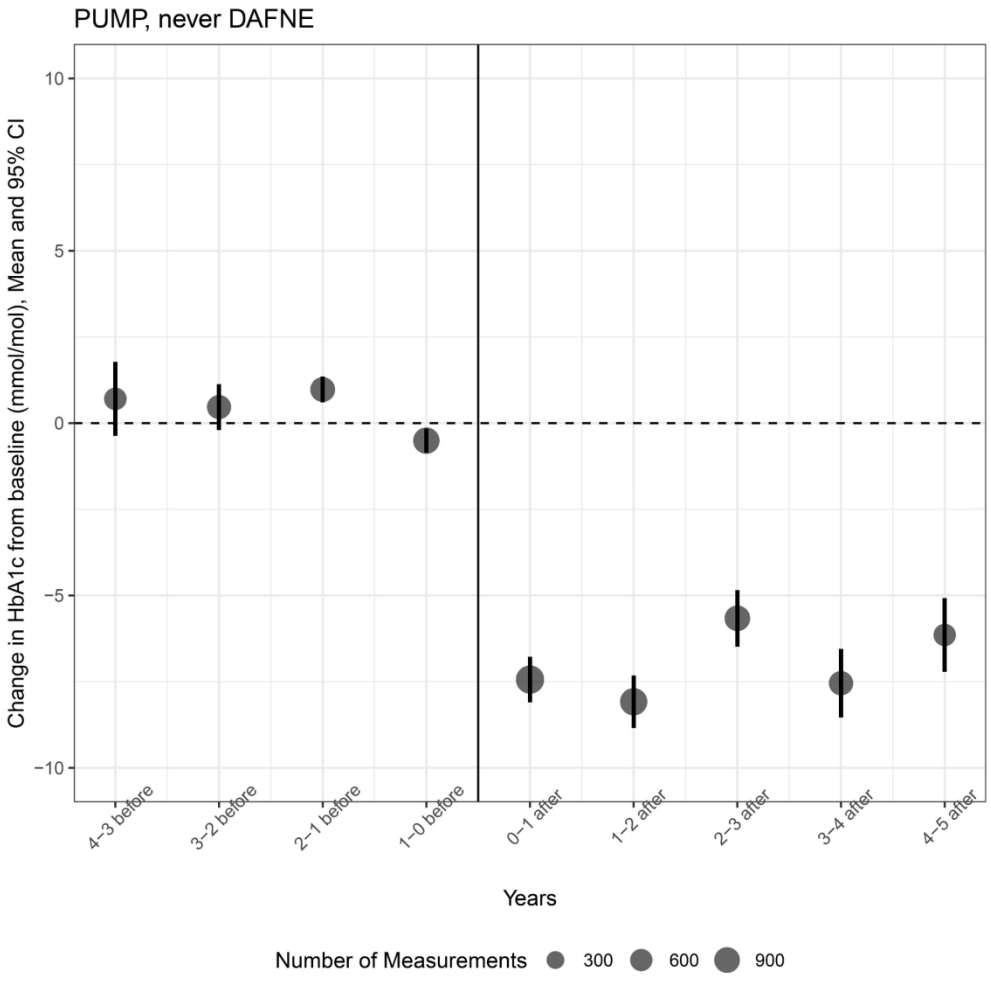

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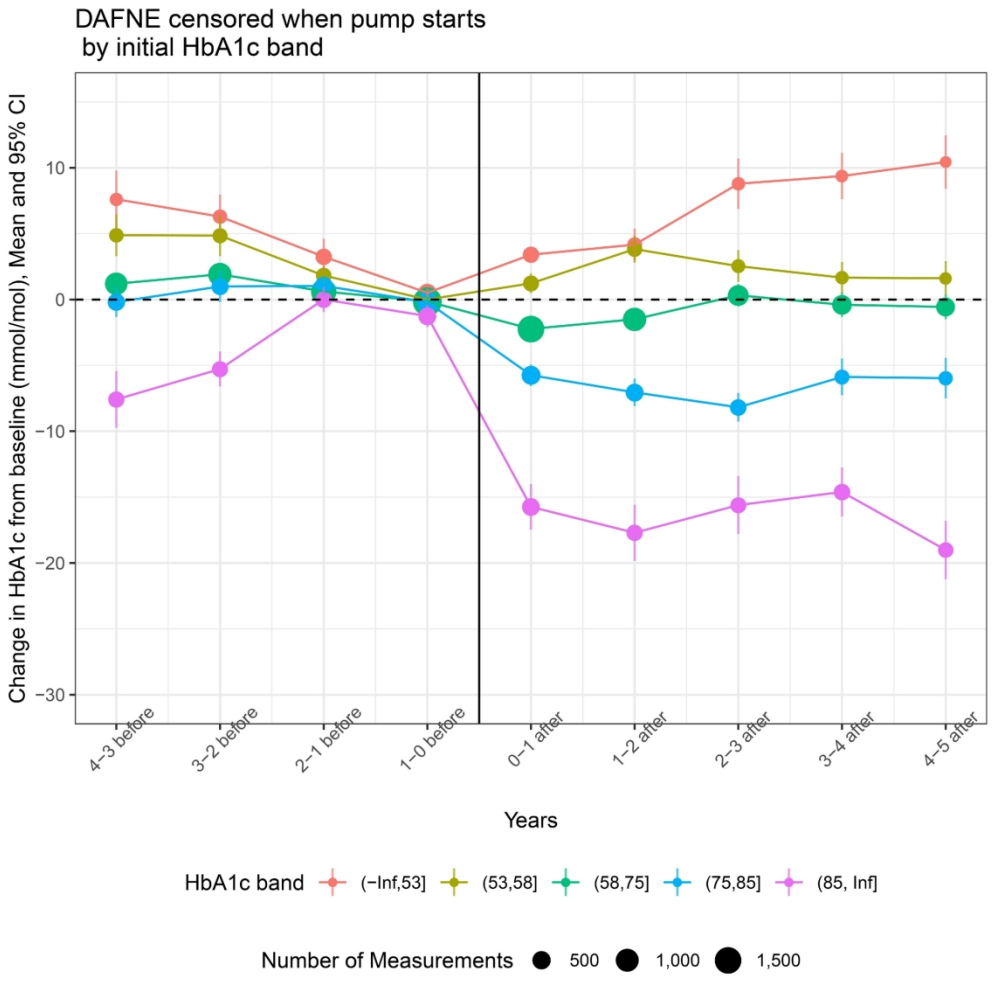

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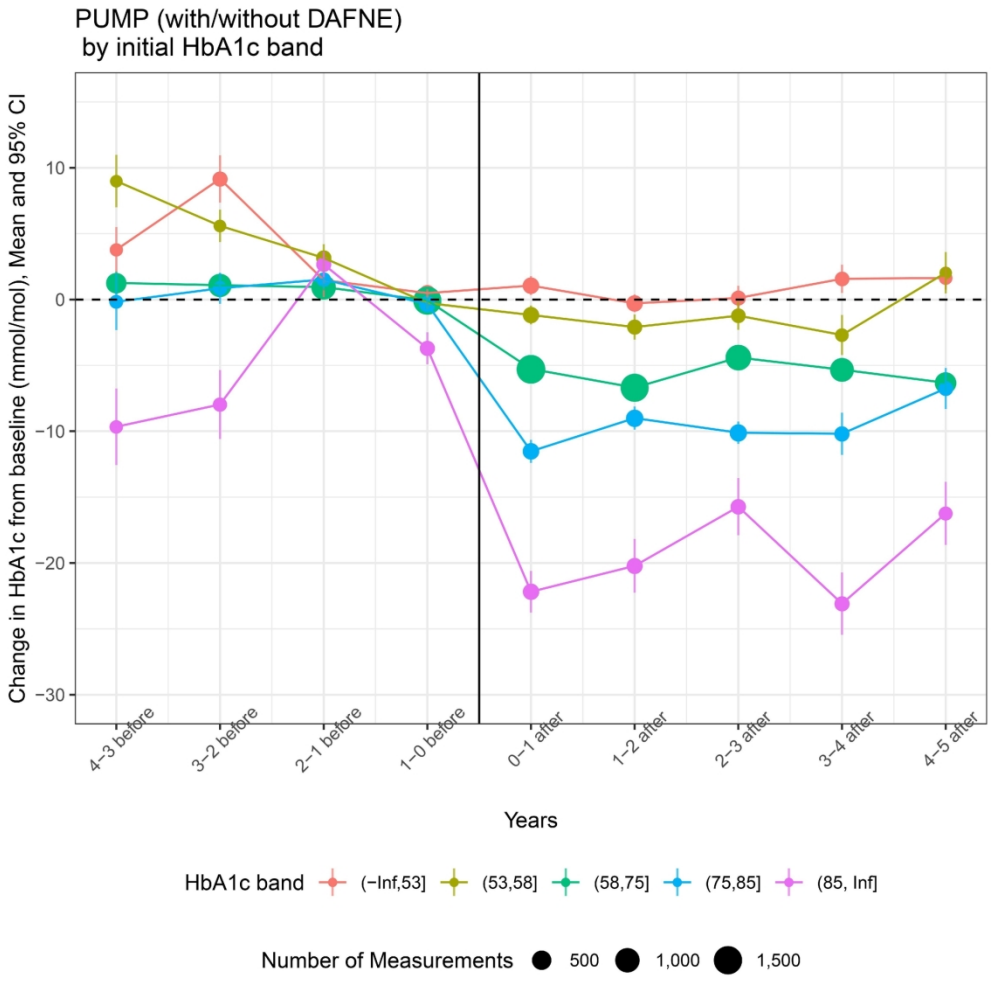

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Research: Care Delivery

The effect of DAFNE ~~Dose Adjustment For Normal Eating~~ ~~DAFNE~~ education, continuous subcutaneous insulin infusion~~CSII~~, or both in a population with t~~T~~ype 1 diabetes in Scotland~~.~~

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What's new?

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Commented [DH2]: Author query: Please check that the authors' affiliations, and the correspondence details, are all correct.

Novelty Statement (100 words) - Currently 155 words

What is already known?

- Both DAFNE (Dose Adjustment For Normal Eating) DAFNE education and continuous subcutaneous insulin infusionCSII lower the levels of HbA$_{1c}$ HbA1c in people with tType 1 diabetes. The size and duration of effect areis not well documented.

What this study has found?

- HbA$_{1c}$ HbA1c decreases with either intervention and the effect lasts at least 5 years. Those with a high HbA$_{1c}$ HbA1c to start with have a very large decrease inof HbA$_{1c}$ HbA1c. following intervention. CSIIContinuous subcutaneous insulin infusion is effective in lowering HbA$_{1c}$ HbA1c whether or not people havewith or without previous DAFNE Dose Adjustment For Normal Eating educationDAFNE already completed a DAFNE course.

What are the clinical implications of the study?

- DAFNEose Adjustment For Normal Eating educationAFNE and CSIIcontinuous subcutaneous insulin infusion are both good options for people with a high HbA$_{1c}$ HbA1c. DAFNE Dose Adjustment For Normal Eating educationDAFNE should not be a prerequisite before CSIIcontinuous subcutaneous insulin infusion. should be considered in those with or without previous DAFNE training.

Abstract

~~Abstract~~

Aim ~~Background and aims:~~

~~The REPOSE study described the relative effectiveness of insulin pumps compared to multiple daily injections over two years. Our~~Thois ~~observational study~~ investigated~~d~~ the effect of DAFNE~~Dose Adjustment For Normal Eating education~~DAFNE ~~and CSII~~continuous subcutaneous insulin infusion ~~i~~in clinical practice.

Methods ~~Methods:~~

Within NHS Lothian, ~~CSII~~continuous subcutaneous insulin infusion ~~started in 2004 and DAFNE Dose Adjustment For Normal Eating education began DAFNE in 2006. there are 4,617 people with Type 1 diabetes over 18 years. CSII started in 2004 and DAFNE in 2006.~~ We extracted anonymi~~z~~sed data from the national database ~~that included~~for all those aged ~~>over~~ 18 years with t~~T~~ype 1 diabetes ~~recorded as~~ having a Dose Adjustment For Normal Eating ~~DAFNE~~ course or ~~CSII~~continuous subcutaneous insulin infusion start date (n = 4,617).

Results ~~Results:~~

In total, 956 persons received~~had~~ DAFNE~~Dose Adjustment For Normal Eating~~ education~~DAFNE~~, and 505 had received an insulin pump, ~~of which~~ 208 of whom had DAFNE ~~Dose Adjustment For Normal Eating~~ education~~DAFNE~~ followed by insulin pump. Mean (SD) HbA_{1c} ~~HbA1c~~ before DAFNE ~~Dose Adjustment For Normal Eating~~ ~~DAFNE~~ education was 68 (15) mmol/mol (8.4% [(1.4%)]) and 66 (13) mmol/mol (8.2% [(1.2%)]) before ~~CSII~~continuous subcutaneous insulin infusion. In the year following DAFNE ~~Dose Adjustment For Normal Eating~~ education~~DAFNE~~, the mean fall in within-person HbA_{1c} ~~HbA1c~~ was 3.8 mmol/mol (95% CI 4.0 to 3.4; (0.3% [(0.4% to 0.3%)]). Those with the poorest control (HbA_{1c} ~~HbA1c~~ ≥ 85 mmol/mol: [(9.9%)]) experienced the largest decline (15.7 mmol/mol: [1.4%]). Those in the lowest HbA_{1c} ~~HbA1c~~ band at initiation (< 53 mmol/mol: [7.0%])) experienced a rise.

In the year following ~~CSII~~continuous subcutaneous insulin infusion initiation there was a mean fall in within-person HbA_{1c} ~~HbA1c~~ of 6.6 mmol/mol ([6.8 to 6.4;] (0.6% [0.6% to 0.6%]). In those with the poorest control (HbA_{1c} ~~HbA1c~~ ≥ 85 mmol/mol: [(9.9%)]), the mean fall in HbA_{1c} ~~HbA1c~~ was 22.2 mmol/mol ([23 to 21;] (2.0% [2.1% to 1.9%]). ~~C~~CSII~~ontinuous subcutaneous insulin infusion~~ effectiveness was not different with or without DAFNE ~~Dose Adjustment For Normal Eating~~ education~~DAFNE~~. The effects of both interventions were sustained over 5~~five~~ years.

Conclusions ~~Conclusions:~~

Both DAFNE ~~Dose Adjustment For Normal Eating~~ education~~DAFNE~~ and insulin pump therapy had the greatest effect on HbA_{1c} ~~HbA1c~~ in those with higher baseline values. There was little difference to attained HbA_{1c} ~~HbA1c~~ when Dose Adjustment For Normal Eating education~~DAFNE~~ was introduced before insulin pump therapy.

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<H1>Introduction

The challenges of managing tType 1 diabetes are well known. People with this condition require insulin for survival and there is a need to achieve glycaemic control that reduces the risk of long-term microvascular and macrovascular complications [1,2] (1) (2). Many people with diabetes in the UK, and indeed throughout the world wide, have higher levels of HbA_{1c} HbA1cs than is recommended [3,4] (3) (4). The use of structured education packages [5] (5) and technologies such as continuous subcutaneous insulin infusion (CSII) provide opportunities to improve their self-management of diabetes and outcomes. The recent Relative Effectiveness of Pumps Over Structured Education (REPOSE) study described the relative effectiveness of CSII compared withto MDI, both with structured education in a 2 two year cluster randomizsed trial [6] (6).

Currently within NHS Lothian there are 4,617 people with tType 1 diabetes aged >over the age of 18 years. A CSII service was started in NHS Lothian in 2004, and the DAFNE (DAFNE (Dose Adjustment For Normal Eating) (DAFNE) education programme was introduced in 2006. We wished aimed to examine the longer term effects of the DAFNE course and CSII therapy on HbA_{1c} HbA_{1c} in our local population.

<H1>Methods

Core data relating to the diabetes care of over > 99% of people with diabetes in the Lothian region areis held on the national diabetes database, SCI Diabetes. After obtaining Caldicott Guardian permission wWe extracted anonymizsed data from this databasesystem that includedfor all those individuals recorded as having a start date for a DAFNE course (n = 956) and those all in receipt of an insulin pump (n = 505), either with (n = 208) or without prior DAFNE (n = 297). From the electronic health records, w We extracted from the electronic health record all the available HbA1cHbA_{1c} data covering time periods both retrospective and prospective to the intervention for these individuals. For each 12-month period before and after the intervention, the median value of multiple measures in that 12-months period was used for eachthat individual was used.

Initial tabulations were made showing the average within-person difference in HbA_{1c} HbA1c across time both retrospective and prospective to the intervention date. Both median and interquartile rangeis (IQR) and means and 95% confidence intervals (95% CI) of the within-person difference for each 12-month block before and after the interventions were summarizsed across all persons. Tabulations and figures were also generated showing these data by strata of age, initial HbA1cHbA_{1c} level, sex and diabetes duration categories. In these tabulations, those who had DAFNE then pump had their HbA_{1c} HbA_{1c} data used for evaluating DAFNE right-censored upon the date of pump receipt. For those receiving an insulin pump, analyses were further stratified by those with and without prior DAFNE.

We chose to describe the response in five different initial HbA_{1c} HbA1c groups. Initially wWe were going to describe the HbA_{1c} HbA1c change based on the HbA_{1c} HbA1c groups described as reported in the previous international comparison [3]published previously (3), but then we added two further extremes of HbA_{1c} HbA1c control tohe give a more detailed analysis of response foron our population.

To confirm whether any apparently significant changes in HbA_{1c} upHbA1c on receipt of the intervention (i.e. those with a confidence intervalsCI for the change not overlapping zero) were statistically significant, we fitted an additive mixed regression model with a random effect for the individual and a first order auto-regressive correlation structure to account for temporal dependencies in these data within individuals. Time was scaled relative to the intervention. All models included age at diagnosis of diabetes, current age group, sex and, initial HbA_{1c} HbA1c band. Significant periods of change were identified as previously described [7] (7). All analyses used the R statistical package.

<H2>Ethical approval

This was an audit/observational study. We obtained Caldicott Guardian permission to review the anonymized data and did not require Ethics committee approval.

<H1>Results

In total, 956 persons had ever had received DAFNE, 505 had ever received an insulin pump, of whomich 208 had DAFNE followed by pump. As summarizsed in Table 1, the median time period of observation in the diabetes registry prior to DAFNE was 10--11 years, was 4 years post-DAFNE and post-pump, and was slightly longer at 6 years for those receiving DAFNE and then going on to a receive a pump. The median number of HbA_{1c} HbA1c values per 12-month period was 1.5 measures per person across this time period.

<INSERT TABLE 1>

<H2>DAFNE

Figure 1aa shows the median and IQR of the within-person difference in HbA_{1c} HbA1c across time compared withto the values in the 12 months prior to the DAFNE initiation date. The mean (95% CI) change across time and the median (IQR) are summarizsed for all persons combined and by sex gender in Table 2. The data are shown in detail by other strata of interest in supplementary Tables S1 and S5.

For DAFNE, it can be seen that the HbA_{1c} HbA1c in the 12 months preceding DAFNE initiation was not significantlymuch different to the values at the time of initiation of DAFNE. Earlier values were slightly higher than at initiation. Then, in the year following DAFNE, the mean fall in within-person HbA_{1c} HbA1c was 3.8 mmol/mol (95% CI 4.0 to 3.4; (0.3% [(0.4% to 0.3%)]) compared to with the HbA_{1c} HbA1c in the

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year prior to DAFNE. Overall, this fall decrease was broadly sustained over time. The decreasefall with DAFNE was slightly greater in women than men (Table 2). There were clear differences in the magnitude of the HbA_{1c} HbA1c change with DAFNE, depending on the HbA_{1c} HbA1c level uponin the at initiation of DAFNE (Fig.ure 2aa, Supplementary Table S1); those with the poorest control (HbA_{1c} HbA1c ≥ 85 mmol/mol [{9.9%]}) experienced the largest decline, with a mean within-person change in HbA_{1c} HbA1c of 15.7 mmol/mol (1.4%), and indeed those in the lowest HbA_{1c} HbA1c band at initiation (< 53 mmol/mmol [{7.0%]}) experienced an increase rise. Difference in change in HbA_{1c} HbA1c with DAFNE did not show a large variation by either age band or and duration (Supplementary Tables S1 and S6), other than in that those aged > 65 years and in those with duration < 10 years duration, who experienced had slightly less change.

<INSERT FIGURE 1>

<INSERT FIGURE 2>

<INSERT TABLE 2>

<H2>CSII

Figure 1 shows the median and IQR of the within-person difference in HbA_{1c} HbA1c across time compared withto the values in the 12 months prior to the CSII initiation date, separated by whether there was (Fig.ure 1bb) or was not (Fig.ure 1cc) prior DAFNE. The mean (95% CI) change across time and the median (IQR) are summarized for all CSII recipients, combined and by sex gender in Table 2. The data are shown in detail by other strata of interest in supplementary Table S2. Data for CSII recipients, separated into those with and without prior DAFNE, are summarized in Supplementary Tables S3 and S7.

For CSII, it can be seen that the HbA_{1c} HbA1c in the 12 months preceding CSII initiation was not significantlymuch different to the values at the time of initiation of CSII. Earlier values were slightly higher than at initiation. Then, in the year following CSII initiation, there was a large mean fall decrease in within-person HbA_{1c} HbA1c of -6.6 mmol/mol [{6.8 to, 6.4}] (0.6%). This decreasefall was sustained over time. The mean fall in HbA_{1c} HbA1c with CSII in the year following initiation was 5.2 mmol/mol [{5.5 to, 4.9}] (0.5%) in men and 7.4 mmol/mol [{7.7 to, 7.2}] (0.7%) in women (Table 2). CSII was effective regardless of whether there was or was not prior DAFNE (Fig.ure 1b,c b&c, Supplementary Table S3). There were clear differences in the magnitude and direction of HbA_{1c} HbA1c change with CSII depending on the HbA_{1c} HbA1c level at initiation, as shown in Fig.ure 2bb and Supplementary Table S2. In those with the poorest control (HbA_{1c} HbA1c ≥ 85 mmol/mol [{9.9%]}), the mean fall in HbA_{1c} HbA1c in the year following receipt of CSII receipt was 22.2 mmol/mol [{23 to, 21.4}] (2.0% [2.1% to 1.9%]), whereas in those with HbA_{1c} HbA1c at initiation < 53 mmol/mol (7.0%) at initiation, values remainedstayed about the same. Difference in change in HbA_{1c} HbA1c with CSII did not show a large variation by age band and wereseemed slightly less in those receiving CSII within 5five years of onset of diabetes.

Adjusted for multiple comparisons within individuals, the changes in HbA_{1c} HbA1c with both DAFNE and CSII in the 4four years following receipt of these interventions were highly significant (all at pP < 0.0001). The regression model showed that the fall in HbA_{1c} HbA1c remained significant when adjusted for other variables. Although in those CSII recipients without prior DAFNE the change in HbA_{1c} HbA1c with CSII was very slightly greater than in those with prior DAFNE (Fig. 1b,cb&c), this was not a significant difference in effect when adjusted for other covariates.

<H1>Discussion

These observational data have shown that, overall, the provision of a DAFNE course or CSII, (with associated education) decreases HbA_{1c} HbA1c. The effect is due mainly to a decrease in those with higher HbA_{1c} HbA1c values before either intervention. In those with an HbA_{1c} HbA1c in a more acceptable range, these interventions have little effect upon overall HbA_{1c} HbA1c and in some individuals with low values of HbA_{1c} HbA1c at initiation there is a slight rise in HbA_{1c} HbA1c with DAFNE. This is not surprising, as the purpose of the interventions in those with tight glycaemic control is to decrease hypoglycaemia and improve quality of life, as demonstrated by the Irish DAFNE Study Group [8] (8), rather than to change overall HbA_{1c} HbA1c. Further work research will explore the impact on these clinical events when data accrue.

We have also demonstrated that the effect of CSII or DAFNE is maintained for at least 5five years after the intervention. We have demonstrated that, within the service provided byin NHS Lothian, introducing CSII without a prior DAFNE course is at least as effective as with a prior DAFNE course. Thus, our data suggest that in those warranting CSII, this should not be delayed if DAFNE is not available.

It is interesting to note that HbA_{1c} HbA1c changed in the few months before initiating stituting DAFNE and before CSII therapy in those who had not previously received DAFNE training. This is likely to reflect the preparation process for starting DAFNE and CSII in Lothian. The CSII preparation involves a detailed review and education about carbohydrate counting and dose adjustment.

Our results are similar towith those of the original DAFNE publication [5], which (5) as they noted a mean HbA_{1c} HbA1c decrease of 5 mmol/mol (0.5%) when compared aftert 1 year. In our analysis, the decrease following DAFNE was 3 mmol/mol (0.3%) in the first year after DAFNE, and this was maintained for 5five years. There are a number of possible explanations for any small minor difference recorded. Many of our population had already been exposed to some carbohydrate CHO counting training, and the mean HbA_{1c} HbA1c at the time of intervention was 68 mmol/mol (8.4%), significantly lower than the 79 mmol/mol (9.4%) in the original DAFNE study. In a 1one year follow-up of 639 people who completed DAFNE training, HbA_{1c} HbA1c decreased from 69 to 66 mmol/mol (8.5% to 8.2%) [9] (9). We have found a similar, prolonged decrease inof HbA_{1c} HbA1c but have also havdemonstratede shown the a different response from those

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who start with a higher or lower HbA1c ~~HbA1c~~. Our longer follow-up demonstrating an ongoing effect on a large cohort of people who have completed DAFNE is also important and adds to a previous smaller report relating to 141 people followed up for 44 months (10).

Our results also contrast with and add to the information from the recent REPOSE study [6] ~~(6)~~. In their cluster randomized controlled trial, ~~they reported a~~ decreases in~~of~~ HbA1c ~~HbA1c~~ at 2~~two~~ years of 4.5 mmol/mol (0.4%) following DAFNE and of 9.3 mmol/mol (0.8%) following CSII were reported. We have been able to analyse our results for 4~~four~~ years before and 5~~five~~ years following the intervention, demonstrating a sustained effect that appears to be~~that seems a little~~ smaller than that noted in the REPOSE trial. Again, this is partly explained by our lower HbA1c ~~HbA1c~~ value at the time of the intervention (75 to 78 mmol/mol [(9.0% to 9.3%)] in REPOSE, 68 to 70 mmol/mol [(8.4% to 8.6%)] in our study). Our population was also different to the REPOSE study population, as the policy in NHS Lothian is to give CSII to those who fulfil the National Institute for Health and Care Excellence criteria for CSII, whereas those individuals were excluded from the REPOSE study.

In addition, we have shown that adding CSII to those who have not taken part in a DAFNE course is at least as effective in lowering HbA1c ~~HbA1c~~ as initiation in those who have received DAFNE. It is important to note, however, that knowledge and application of carbohydrate counting is assessed and addressed for each individual as part of the CSII referral and initiation process within NHS Lothian, and that people would not be considered for a pump without the appropriate skills. We have, however, also demonstrated that adding CSII to those who have already received DAFNE provides further added benefit in lowering HbA1c ~~HbA1c~~.

A strength of this analysis is the use of routine clinical data, collected as part of clinical care, for the whole population in our area over a 10~~ten~~-year period. Our study population is sufficiently large to enable a detailed analysis and we do not believe there has been any selection bias as those studied were identified on our comprehensive, population-wide database. Previous studies have involved far fewer individuals. We have also provided information on a group of individuals selected as wanting these interventions, a better reflection of the effects in real clinical practice.

During the time period of this analysis there has been a change of overall glycaemic control in the whole population with t~~T~~ype 1 diabetes in Lothian. Our regression analysis has, however, enabled us to ensure that the changes in HbA1c ~~HbA1c~~ within initiation of DAFNE and CSII were not attributable to any ongoing background downward trend in HbA1c ~~HbA1c~~. Indeed, apart from the period immediately preceding and immediately after~~post~~ the intervention, ~~the~~ HbA1c ~~HbA1c~~ control was ~~has been~~ stable both ~~in the~~ before and after the interventions in this group.

A limitation of our study is that we have only investigated the effect of our interventions upon HbA1c ~~HbA1c~~. We have not measured quality of life indicators, and do not believe that our information relating to hypoglycaemia is sufficiently accurate to be included in this analysis. It ~~One~~ must therefore be recognized that we are ~~therefore~~ failing to report on two very important aspects of diabetes care.

Despite these limitations, we ~~can~~ conclude that both interventions are effective in lowering HbA1c ~~HbA1c~~. The effects are greater in those with a higher HbA1c ~~HbA1c~~, and in our experience it is not necessary to have received~~had~~ a DAFNE course before introducing CSII. These data provide further information to influence guidelines and health policy.

<H2>Funding sources

None.

~~**Ethics Statement**~~

~~This was an audit/observational study. We obtained Caldicott Guardian permission (as stated in the text) to review the anonymised data and did not require Ethics committee approval.~~

~~**Acknowledgements**~~

<H2>Competing ~~nflict of I~~Interests

~~HMC receives research support and honorarium and is also a member of the advisory panels or speaker's bureaus for Sanofi Aventis, Regeneron, Novartis Pharmaceuticals, Novo-Nordisk and Eli Lilly. HMC also receives or has recently received a non-binding research support from Pfizer Inc., and AstraZeneca LP and Novo-Nordisk. HMC is a shareholder of Roche Pharmaceuticals and Bayer.~~

H.M.C. has received grants, personal fees and non-financial support from Eli Lilly & Company, grants from Pfizer Inc., grants from Boehringer Ingelheim, grants from AstraZeneca LP, grants, personal fees and non-financial support from Sanofi, non-financial support from Novartis Pharmaceuticals, personal fees and non-financial support from Regeneron, has received grants and holds shares at Roche Pharmaceuticals, is a shareholder in Bayer, and has received non-financial support from Sanofi Aventis, outside the submitted work. All of the other authors declare that there is no duality of interest associated with their contribution to this manuscript. The study sponsors had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

<H2>~~Ethical approval~~

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~~This was an audit/observational study. We obtained Caldicott Guardian permission to review the anonymized data and did not require Ethics committee approval.~~

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Table 1: Characteristics of each group

	Ever DAFNE	Ever CSII	DAFNE then CSII
N (%)	956 (76.3)	505 (40.3)	208 (16.6)
WomenFemale, N n (%)	523 (54.7)	307 (60.8)	121 (58.2)
Age of Oonset, median (IQR)	20.1 (11.9, 30.8)	14.8 (9.0, 24.9)	16.4 (10.2, 26.9)
Diabetes dDuration at pPump iInitiation, median (IQR)		19.8 (11.3, 28.3)	21.1 (12.5, 27.3)
Diabetes dDuration at DAFNE iInitiation, median (IQR)	15.9 (7.4, 24.9)		18.3 (9.7, 25.0)
Initial HbA_{1c} HbA1c (mmol/mol), median (IQR)	68 (60, 78)	66 (60, 75)	68 (60, 77)
Initial HbA_{1c} HbA1c (%), median (IQR)	8.4 (7.6, 9.3)	8.2 (7.6, 9.0)	8.3 (7.6, 9.2)
Initial HbA_{1c} HbA1c bBand 1, nN (%)	103 (11.4)	23 (11.1)	23 (11.1)
Initial HbA_{1c} HbA1c bBand 2, nN (%)	95 (10.6)	20 (9.6)	20 (9.6)
Initial HbA_{1c} HbA1c bBand 3, nN (%)	413 (45.9)	128 (61.5)	128 (61.5)
Initial HbA_{1c} HbA1c bBand 4, nN (%)	160 (17.8)	23 (11.1)	23 (11.1)
Initial HbA_{1c} HbA1c bBand 5, nN (%)	129 (14.3)	14 (6.7)	14 (6.7)
Pump Sstart yYear, (minimum, maximum)		2004, 2017	2009, 2017
DAFNE Sstart yYear, (minimum, maximum)	2002, 2018		2006, 2016
Time before CSII, median (IQR)		11.5 (15.1, 7.1)	10.6 (14.1, 7.3)
Time before DAFNE, median (IQR)	10.5 (15.1, 5.6)		10.6 (14.1, 7.3)
Time after CSII, median (IQR)		4.3 (2.9, 6.3)	4.3 (2.2, 5.1)
Time after DAFNE, median (IQR)	4.4 (2, 7)		6.2 (4.4, 8.1)

CSII, continuous subcutaneous insulin infusion; DAFNE, Dose Adjustment For Normal Eating

Band 1 < 53 mmol/mol (< 7.0%); bBand 2: 53 to 57 mmol/mol (7.0% to 7.4%); bBand 3: 58 to 74 mmol/mol (7.5% to 8.9%); bBand 4: 75 to 84 mmol/mol (9.0% to 9.9%); bBand 5 ≥ 85 mmol/mol (≥ 10%)

Table 2 Difference in $HbA1_C$ (mmol/mol) with respect to intervention initiation date. (Results in % units are shown in Supplementary Table S4)

Difference with respect to DAFNE initiation date overall									
Years since DAFNE	-4	-3	-2	-1	0	1	2	3	4
n median ([IQR])* mean (95% CI)**	2,058 0.4 [0.1, 0.7] -0.5 (-6.0 to 6.0)	2,225 1.5 [1.2, 1.7] 0.0 (-4.5 to 6.0)	2,775 1.1 [0.9, 1.2] 0.0 (-2.0 to 3.0)	4,004 -0.2 [-0.3, -0.1] 0.0 (-1.0 to 1.0)	3,163 -3.8 [-4.0, -3.6] -3.0 (-8.5 to 2.0)	2,340 -3.7 [-4.0, -3.4] -2.5 (-10.5 to 3.5)	1,754 -3.2 [-3.5, -2.8] -2.5 (-10.0 to 5.0)	1,502 -3.6 [-4.0, -3.2] -3.0 (-12.0 to 5.0)	1,233 -4.6 [-5.1, -4.2] -3.0 (-13.5 to 5.0)
Difference with respect to DAFNE initiation date by sex									
Female Women	1,149 0.4 [-0.1, 0.8] -0.5 (-7.0 to 6.5)	1,251 1.4 [1.1, 1.8] 0.5 (-5.0 to 6.0)	1,541 1.0 [0.8, 1.3] 0.0 (-2.0 to 2.5)	2,222 -0.2 [-0.3, -0.1] 0.0 (-1.0 to 0.5)	1,792 -4.4 [-4.7, -4.1] -3.5 (-9.0 to 1.6)	1,358 -5.2 [-5.6, -4.8] -3.5 (-12.0 to 3.0)	1,026 -4.0 [-4.5, -3.5] -3.5 (-10.5 to 4.0)	882 -3.7 [-4.3, -3.2] -3.0 (-13.0 to 5.0)	745 -4.5 [-5.1, -3.9] -3.0 (-14.0 to 5.0)
Menale	909 0.4 [0.0, 0.8] -0.5 (-5.0 to 5.0)	974 1.5 [1.2, 1.9] 0.0 (-4.0 to 6.0)	1,234 1.1 [0.9, 1.3] 0.0 (-1.5 to 3.0)	1,782 -0.2 [-0.3, -0.1] 0.0 (-1.5 to 1.0)	1,371 -3.1 [-3.4, -2.8] -3.0 (-7.5 to 3.0)	982 -1.7 [-2.1, -1.3] -1.0 (-6.5 to 5.0)	728 -2.0 [-2.5, -1.5] -1.5 (-9.2 to 5.0)	620 -3.4 [-4.0, -2.9] -3.0 (-9.5 to 4.5)	488 -4.9 [-5.6, -4.2] -2.5 (-13.0 to 4.0)
Difference with respect to CSII initiation date overall									
Years since CII	-4	-3	-2	-1	0	1	2	3	4
n median ([IQR])* mean (95% CI)**	1,102 0.7 [0.3, 1.1] 1.0 (-5.5 to 6.3)	1,534 1.5 [1.2, 1.8] 1.5 (-4.0 to 6.0)	1,843 1.5 [1.4, 1.7] 0.2 (-1.3 to 2.8)	2,521 -0.4 [-0.4, -0.3] 0.0 (-1.8 to 1.0)	2,715 -6.6 [-6.8, -6.4] -5.5 (-10.8 to -0.5)	2,583 -7.3 [-7.5, -7.1] -6.7 (-12.0 to -1.0)	2,116 -5.8 [-6.1, -5.6] -5.1 (-12.0 to 0.3)	1,699 -7.2 [-7.5, -6.9] -5.5 (-14.3 to 0.5)	1,278 -6.1 [-6.4, -5.8] -5.3 (-12.2 to 0.3)
Difference with respect to CSII initiation date by sex									
Female Women	695 -0.1 [-0.6, 0.4] 1.0 (-7.0 to 6.0)	1,012 1.4 [1.0, 1.8] 2.0 (-4.0 to 5.5)	1,142 1.3 [1.2, 1.5] 0.1 (-1.5 to 2.8)	1,474 -0.3 [-0.4, -0.2] 0.0 (-1.7 to 1.4)	1,709 -7.4 [-7.7, -7.2] -6.5 (-11.5 to -1.5)	1,659 -8.0 [-8.3, -7.7] -7.0 (-13.2 to -1.7)	1,379 -6.3 [-6.6, -6.0] -5.0 (-13.0 to 0.3)	1,128 -8.1 [-8.5, -7.7] -5.7 (-16.0 to 0.5)	881 -6.8 [-7.3, -6.4] -6.0 (-13.5 to -0.2)
Menale	407 2.1 [1.6, 2.6] 1.0 (-3.5 to 7.0)	522 1.8 [1.4, 2.2] 1.0 (-4.0 to 6.5)	701 1.8 [1.6, 2.1] 0.8 (-1.0 to 3.0)	1,047 -0.4 [-0.5, -0.3] -0.5 (-2.0 to 0.5)	1,006 -5.2 [-5.5, -4.9] -4.0 (-10.0 to 1.4)	924 -6.1 [-6.4, -5.8] -5.0 (-11.0 to -0.5)	737 -5.0 [-5.4, -4.7] -5.2 (-9.7 to 0.0)	571 -5.5 [-5.9, -5.1] -5.0 (-11.2 to 0.0)	397 -4.5 [-4.9, -4.1] -4.0 (-8.5 to 0.3)

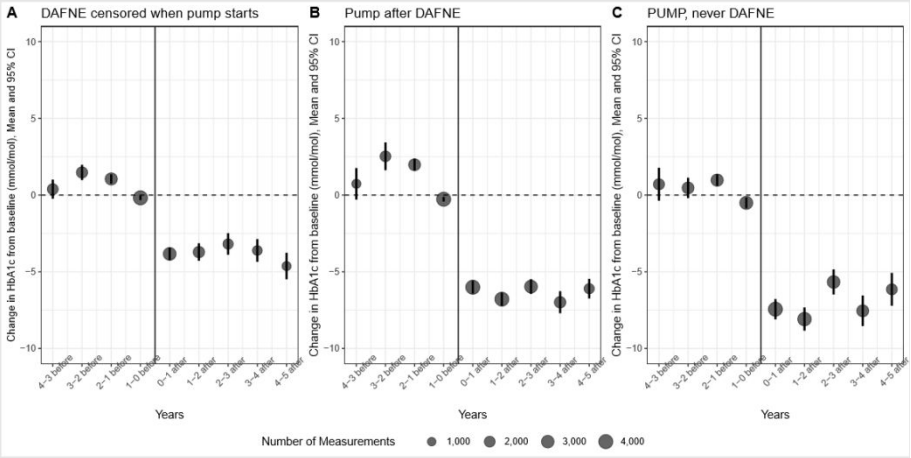
CSII, continuous subcutaneous insulin infusion; DAFNE, Dose Adjustment For Normal Eating

HbA_{1c} $HbA1_c$ values in International Federation of Clinical Chemistry IFCC mmol/mol units

*IQR = interquartile range in square brackets

**95% CI = 95% confidence interval in round brackets

FIGUREigure 1 Median dDifference in HbA_{1c} ~~HbA1c~~ over time compared with~~to~~ HbA_{1c} ~~HbA1c~~ at dDate of iintervention



Commented [DH10]: Author query: For Figure 1, add details of parts (A), (B) and (C) to the Figure 1 legend.

FIGUREigure 2 Median dDifference in HbA_{1c} HbA1c over time compared withto HbA_{1c} HbA1c at dDate of iintervention by HbA_{1c} HbA1c band at date of intervention

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<H1>Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Difference in $HbA1_C$ over time with respect to DAFNE initiation date.

Table S2 Difference in $HbA1_C$ across time with respect to CSII initiation date by strata.

Table S3 Difference in $HbA1_C$ across time with respect to CSII initiation date stratified by DAFNE.

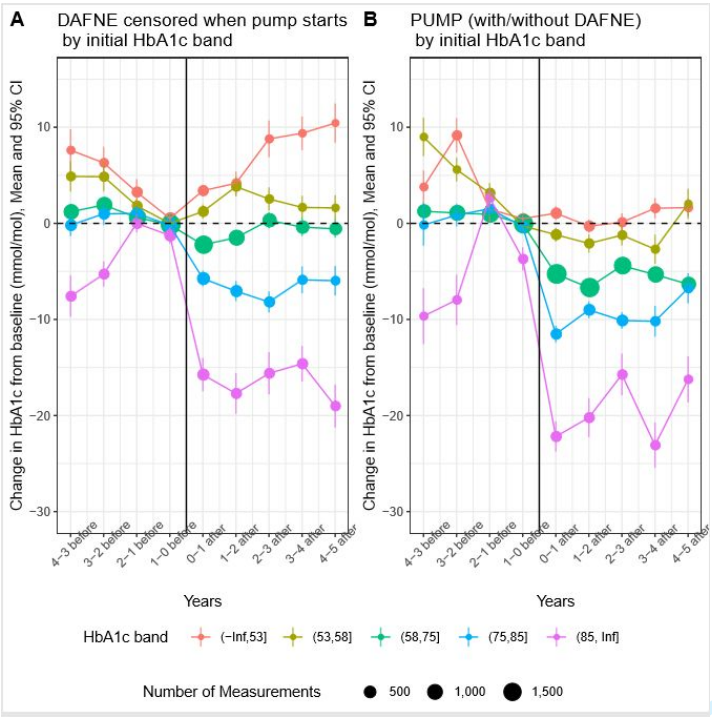
Table S4 Difference in $HbA1_C$ with respect to intervention initiation date ($HbA1_C$ in percentage units).

Table S5 Difference in $HbA1_C$ over time with respect to DAFNE initiation date ($HbA1_C$ percentage units).

Table S6 Difference in $HbA1_C$ across time with respect to CSII initiation date by strata ($HbA1_C$ in percentage units).

Table S7 Difference in $HbA1_C$ across time with respect to CSII initiation date stratified by DAFNE ($HbA1_C$ in percentage units).

<TYPESETTER: Ensure that the Supporting Information, which follows on from here, is not published with the main text.>


A
DAFNE censored when pump starts by initial HbA1c band
B
PUMP (with/without DAFNE) by initial HbA1c band
Change in HbA1c from baseline (mmol/mol), Mean and 95% CI
10
0
−10
−20
−30
4−3 before
3−2 before
2−1 before
1−0 before
0−1 after
1−2 after
2−3 after
3−4 after
4−5 after
Years
HbA1c band
(−Inf,53]
(53,58]
(58,75]
(75,85]
(85, Inf]
Number of Measurements
500
1,000
1,500

Supplementary Table 1 Difference in $HbA1_c$ over time with respect to DAFNE initiation date

All DAFNE recipients									
Years since DAFNE	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
n median[IQR]* mean(95%CI)**	2,058 0.4 [0.1, 0.7] -0.5 (-6.0,6.0)	2,225 1.5 [1.2, 1.7] 0.0 (-4.5,6.0)	2,775 1.1 [0.9, 1.2] 0.0 (-2.0,3.0)	4,004 -0.2 [-0.3, -0.1] 0.0 (-1.0,1.0)	3,163 -3.8 [-4.0, -3.6] -3.0 (-8.5,2.0)	2,340 -3.7 [-4.0, -3.4] -2.5 (-10.5,3.5)	1,754 -3.2 [-3.5, -2.8] -2.5 (-10.0,5.0)	1,502 -3.6 [-4.0, -3.2] -3.0 (-12.0,5.0)	1,233 -4.6 [-5.1, -4.2] -3.0 (-13.5,5.0)
All DAFNE recipients stratified by $HbA1_C$									
$HbA1_c$	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
(-Inf,53]	154 7.6 [6.5, 8.7] 5.5 (-0.5,11.5)	211 6.3 [5.4, 7.2] 4.0 (-0.5,7.5)	337 3.3 [2.6, 3.9] 0.0 (-1.5,3.0)	479 0.5 [0.4, 0.7] 0.0 (-1.0,0.5)	334 3.4 [3.1, 3.7] 3.0 (0.0,6.0)	236 4.2 [3.5, 4.8] 2.5 (-1.5,8.0)	158 8.8 [7.8, 9.8] 6.0 (1.0,21.5)	122 9.4 [8.5, 10.3] 9.5 (2.4,16.0)	88 10.4 [9.4, 11.5] 13.0 (4.0,16.0)
(53,58]	220 4.9 [4.1, 5.7] 1.8 (-2.0,6.6)	255 4.9 [4.1, 5.6] 2.0 (-1.5,7.8)	285 1.8 [1.5, 2.2] 0.5 (-1.0,4.0)	479 0.0 [-0.2, 0.2] 0.0 (-1.0,0.0)	311 1.2 [0.8, 1.6] 1.0 (-4.0,5.0)	268 3.8 [3.3, 4.3] 2.0 (-1.0,5.9)	188 2.5 [1.9, 3.2] 0.5 (-3.0,5.5)	159 1.7 [1.1, 2.3] 2.0 (-4.0,5.0)	116 1.6 [0.9, 2.3] 2.0 (-3.0,5.5)
(58,75]	943 1.2 [0.8, 1.6] 0.0 (-5.0,5.0)	1,048 1.9 [1.6, 2.3] 1.0 (-3.5,6.0)	1,317 0.6 [0.4, 0.8] 0.0 (-1.5,2.5)	1,863 -0.1 [-0.2, -0.1] 0.0 (-1.0,1.0)	1,516 -2.2 [-2.5, -2.0] -2.8 (-7.0,1.5)	1,047 -1.5 [-1.8, -1.2] -2.0 (-7.0,3.0)	749 0.3 [-0.1, 0.8] -1.5 (-6.0,6.0)	623 -0.4 [-0.9, 0.1] -1.0 (-6.0,5.5)	544 -0.6 [-1.0, -0.1] -1.5 (-7.0,4.5)
(75,85]	411 -0.2 [-0.8, 0.4] -2.0 (-6.0,5.0)	392 1.0 [0.4, 1.6] -0.8 (-6.0,6.5)	474 1.0 [0.7, 1.4] 0.0 (-2.0,2.0)	731 -0.2 [-0.3, 0.0] 0.0 (-1.5,0.5)	551 -5.7 [-6.2, -5.3] -6.0 (-12.8,-1.5)	454 -7.1 [-7.6, -6.5] -8.5 (-14.5,0.0)	348 -8.2 [-8.7, -7.6] -9.0 (-18.0,-1.0)	246 -5.9 [-6.6, -5.2] -8.0 (-13.0,1.0)	208 -6.0 [-6.7, -5.2] -7.0 (-14.0,1.2)
(85, Inf]	330 -7.6 [-8.7, -6.5] -7.5 (-17.0,3.8)	319 -5.3 [-6.0, -4.6] -4.0 (-10.5,1.0)	362 0.0 [-0.5, 0.5] 0.0 (-4.5,3.5)	452 -1.3 [-1.7, -0.8] 0.0 (-3.0,1.5)	451 -15.7 [-16.6, -14.9] -13.0 (-29.0,-6.2)	335 -17.7 [-18.8, -16.6] -17.0 (-31.0,-6.0)	311 -15.6 [-16.7, -14.5] -12.0 (-29.5,-2.2)	352 -14.6 [-15.6, -13.7] -15.0 (-26.0,-2.0)	277 -19.0 [-20.1, -17.9] -18.0 (-28.0,-6.0)
All DAFNE recipients stratified by age									
Age group	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
(13,19]	372 -3.1 [-4.0, -2.2] -3.8 (-11.0,6.0)	278 1.3 [0.3, 2.3] 0.2 (-8.0,6.2)	202 2.2 [1.0, 3.3] 0.0 (-3.0,3.0)	151 1.5 [1.0, 2.0] 0.0 (-0.5,2.0)	72 4.3 [3.1, 5.5] 4.0 (-3.8,11.9)	9 9.2 [2.1, 16.3] 4.0 (-4.5,30.0)	NA	NA	NA
(19,25]	244 4.7 [3.3, 6.1] 1.8 (-4.2,10.2)	290 3.5 [2.6, 4.5] 3.5 (-6.0,9.0)	421 2.0 [1.5, 2.4] 0.0 (-3.0,4.0)	676 -0.5 [-0.8, -0.3] 0.0 (-2.0,0.0)	460 -3.6 [-4.5, -2.8] -2.5 (-8.0,7.0)	321 -2.8 [-3.9, -1.7] -1.0 (-9.5,9.0)	221 -2.6 [-3.7, -1.4] -2.0 (-10.0,6.5)	184 -6.6 [-8.2, -4.9] -3.0 (-25.0,6.0)	112 -1.4 [-3.4, 0.7] 2.0 (-18.5,13.0)
(25,45]	839 0.5 [0.2, 0.9] -0.5 (-6.0,5.0)	918 1.1 [0.7, 1.5] 0.0 (-4.0,5.5)	1,264 1.2 [1.0, 1.4] 0.0 (-1.5,2.5)	1,848 -0.2 [-0.3, -0.1] 0.0 (-1.0,1.0)	1,514 -4.5 [-4.7, -4.2] -4.0 (-10.0,2.0)	1,165 -4.6 [-5.0, -4.2] -3.0 (-12.0,3.0)	847 -4.8 [-5.3, -4.2] -4.0 (-12.0,5.0)	718 -4.7 [-5.2, -4.2] -4.5 (-12.0,4.5)	564 -7.8 [-8.5, -7.1] -7.0 (-15.0,3.0)
(45,65]	556 0.2 [-0.4, 0.7] -0.5 (-5.5,5.0)	671 0.9 [0.6, 1.3] 0.0 (-4.0,5.0)	789 0.1 [-0.1, 0.3] 0.0 (-2.0,3.0)	1,146 -0.1 [-0.2, 0.0] 0.0 (-1.0,1.0)	926 -3.9 [-4.2, -3.6] -3.0 (-7.0,1.0)	698 -2.8 [-3.1, -2.4] -2.0 (-8.0,2.5)	560 -1.4 [-1.9, -0.9] -1.0 (-7.0,5.0)	480 -0.9 [-1.4, -0.3] -2.0 (-8.5,7.0)	457 -1.3 [-1.8, -0.8] -2.0 (-7.5,5.0)
(65, Inf]	47 5.2 [3.9, 6.5] 3.5 (1.0,6.0)	68 3.7 [2.8, 4.6] 2.5 (-0.5,7.5)	99 0.8 [0.5, 1.2] 0.5 (0.0,2.5)	183 -0.7 [-0.9, -0.4] 0.0 (-2.0,0.0)	191 -1.9 [-2.3, -1.5] -2.0 (-5.5,1.0)	147 -3.9 [-4.6, -3.2] -3.0 (-6.5,1.0)	126 -1.8 [-3.0, -0.6] -1.0 (-5.6,2.0)	120 -3.6 [-4.8, -2.4] -1.5 (-8.0,5.0)	100 -5.4 [-6.7, -4.1] -2.2 (-12.0,3.2)
All DAFNE recipients stratified by duration									
Duration	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
(-Inf,5]	468 0.5 [-0.5, 1.4] -2.0 (-8.5,6.5)	512 1.4 [0.6, 2.1] -0.5 (-8.6,8.0)	713 2.2 [1.7, 2.7] 0.0 (-2.0,3.0)	927 -0.2 [-0.3, 0.0] 0.0 (-0.5,1.0)	605 0.2 [-0.4, 0.8] 0.5 (-4.5,8.0)	387 2.9 [2.0, 3.9] 3.5 (-2.2,13.0)	204 3.6 [2.2, 4.9] 2.0 (-5.1,13.9)	94 -0.2 [-2.3, 1.9] 1.0 (-7.4,12.0)	10 -4.0 [-12.9, 4.9] -20.0 (-20.0,27.0)
(5,10]	389	408	501	665	463	359	278	269	249

	0.4 [-0.4, 1.3] 1.0 (-7.0,7.5)	2.4 [1.7, 3.0] 1.5 (-4.0,6.5)	1.1 [0.8, 1.4] 0.0 (-2.0,3.0)	-0.1 [-0.3, 0.1] 0.0 (-1.5,0.5)	-2.8 [-3.4, -2.3] -2.5 (-7.0,2.0)	-3.0 [-3.7, -2.4] -1.0 (-7.2,4.5)	-3.2 [-4.2, -2.1] -2.0 (-11.5,7.9)	0.4 [-0.6, 1.4] 2.0 (-8.0,10.5)	-1.3 [-2.4, -0.3] -1.0 (-9.0,6.5)
(10,15]	327 -1.0 [-1.7, -0.4] -2.0 (-8.0,4.0)	315 0.4 [-0.3, 1.1] -1.0 (-5.5,5.5)	339 0.4 [0.1, 0.8] 0.0 (-2.0,3.5)	536 -0.7 [-1.0, -0.5] 0.0 (-1.5,1.0)	439 -6.7 [-7.3, -6.1] -5.0 (-11.5,1.0)	338 -8.2 [-9.0, -7.4] -6.0 (-17.8,2.4)	254 -5.5 [-6.3, -4.7] -3.5 (-11.0,0.5)	286 -5.5 [-6.3, -4.7] -4.5 (-13.0,2.5)	204 -7.8 [-8.8, -6.9] -9.5 (-15.0,2.0)
(15,20]	303 1.4 [0.8, 2.0] 0.0 (-4.0,5.0)	332 3.0 [2.5, 3.5] 1.0 (-2.6,7.5)	406 0.2 [-0.1, 0.5] 0.0 (-1.5,2.0)	570 0.0 [-0.2, 0.2] 0.0 (-1.5,1.0)	511 -5.8 [-6.3, -5.2] -4.0 (-9.0,1.0)	368 -6.4 [-7.2, -5.6] -5.0 (-14.0,2.0)	230 -8.3 [-9.3, -7.4] -6.2 (-14.0,1.0)	190 -10.0 [-11.0, -9.1] -6.5 (-26.0,2.0)	143 -6.6 [-8.0, -5.2] -5.5 (-12.5,5.0)
(20, Inf]	571 0.5 [0.2, 0.9] 0.0 (-4.0,5.0)	658 0.7 [0.5, 1.0] 0.0 (-3.0,4.4)	816 0.7 [0.6, 0.9] 0.0 (-1.5,3.0)	1,306 -0.1 [-0.2, 0.0] 0.0 (-1.0,0.5)	1,145 -4.4 [-4.7, -4.1] -4.0 (-9.5,0.5)	888 -4.1 [-4.4, -3.7] -3.5 (-10.0,1.0)	788 -2.7 [-3.1, -2.3] -2.5 (-9.0,4.0)	663 -3.1 [-3.6, -2.6] -3.0 (-11.0,5.0)	627 -4.5 [-5.1, -3.9] -2.5 (-13.2,4.0)

$HbA1_c$ values in IFCC mmol/mol units

* IQR = interquartile range in square brackets

** 95% CI = 95% confidence interval in round brackets

Supplementary Table 2 Difference in $HbA1_c$ across time with respect to CSII initiation date by strata

All CSII recipients									
Years since CII	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
n median[IQR]* mean(95%CI)**	1,102 0.7 [0.3, 1.1] 1.0 (-5.5,6.3)	1,534 1.5 [1.2, 1.8] 1.5 (-4.0,6.0)	1,843 1.5 [1.4, 1.7] 0.2 (-1.3,2.8)	2,521 -0.4 [-0.4, -0.3] 0.0 (-1.8,1.0)	2,715 -6.6 [-6.8, -6.4] -5.5 (-10.8,-0.5)	2,583 -7.3 [-7.5, -7.1] -6.7 (-12.0,-1.0)	2,116 -5.8 [-6.1, -5.6] -5.1 (-12.0,0.3)	1,699 -7.2 [-7.5, -6.9] -5.5 (-14.3,0.5)	1,278 -6.1 [-6.4, -5.8] -5.3 (-12.2,0.3)
All CSII recipients stratified by $HbA1_c$									
$HbA1_c$	**-48 to -36**	**-36 to -24**	**-24 to -12**	**-12 to 0**	**0 to 12**	**12 to 24**	**24 to 36**	**36 to 48**	**48 to 60**
(-Inf,53]	126 3.8 [2.9, 4.7] 1.0 (-1.8,8.2)	217 9.2 [8.2, 10.1] 6.5 (1.0,9.8)	221 1.5 [0.8, 2.1] -0.6 (-3.8,2.5)	291 0.5 [0.3, 0.6] 0.0 (-0.7,1.0)	293 1.1 [0.7, 1.4] 0.8 (-3.5,6.2)	286 -0.3 [-0.6, 0.1] 0.2 (-2.0,2.5)	206 0.1 [-0.4, 0.6] 1.8 (-4.0,4.3)	187 1.6 [1.0, 2.1] -0.5 (-3.0,6.3)	140 1.6 [1.2, 2.1] 1.4 (-3.3,4.0)
(53,58]	100 9.0 [8.0, 10.0] 5.3 (2.2,13.7)	104 5.6 [5.0, 6.2] 6.2 (-1.0,11.8)	228 3.2 [2.6, 3.7] 0.1 (-0.5,3.5)	261 -0.3 [-0.5, 0.0] -0.3 (-2.5,0.4)	282 -1.2 [-1.5, -0.8] -2.3 (-5.0,2.2)	214 -2.1 [-2.6, -1.6] -3.0 (-6.0,0.0)	190 -1.2 [-1.8, -0.7] -2.0 (-7.0,2.2)	143 -2.7 [-3.5, -1.9] -2.0 (-10.7,0.8)	96 2.0 [1.2, 2.8] 2.2 (-3.1,4.0)
(58,75]	590 1.3 [0.8, 1.7] 1.2 (-4.0,6.2)	868 1.1 [0.8, 1.4] 1.0 (-3.6,4.5)	1,004 0.9 [0.8, 1.1] 0.1 (-1.0,2.5)	1,462 -0.1 [-0.1, 0.0] 0.0 (-1.5,1.3)	1,557 -5.3 [-5.4, -5.1] -5.0 (-9.5,-0.7)	1,464 -6.7 [-6.9, -6.5] -7.0 (-11.8,-1.7)	1,147 -4.4 [-4.7, -4.2] -4.5 (-9.5,1.0)	930 -5.3 [-5.6, -5.0] -4.9 (-11.0,1.0)	687 -6.3 [-6.7, -6.0] -6.0 (-12.4,0.0)
(75,85]	151 -0.2 [-1.3, 0.9] -1.3 (-6.8,3.5)	176 0.9 [0.3, 1.5] 1.7 (-3.5,4.9)	185 1.5 [1.2, 1.9] 1.7 (-1.0,3.3)	292 -0.3 [-0.6, -0.1] 0.0 (-2.2,2.3)	299 -11.5 [-12.0, -11.1] -10.8 (-16.8,-4.7)	350 -9.0 [-9.4, -8.6] -9.5 (-13.5,-2.2)	341 -10.1 [-10.5, -9.7] -10.5 (-15.0,-4.5)	223 -10.2 [-11.0, -9.4] -11.0 (-17.0,-5.5)	196 -6.8 [-7.5, -6.0] -5.7 (-11.5,-5.0)
(85, Inf]	135 -9.7 [-11.1, -8.2] -11.7 (-22.0,2.5)	169 -8.0 [-9.3, -6.6] -11.7 (-18.5,1.5)	205 2.7 [2.2, 3.2] 1.7 (-1.4,5.3)	215 -3.7 [-4.3, -3.1] -2.6 (-5.5,0.5)	284 -22.2 [-23.0, -21.4] -21.3 (-27.1,-15.2)	269 -20.2 [-21.3, -19.2] -19.3 (-30.0,-10.5)	232 -15.7 [-16.8, -14.6] -20.2 (-27.2,-8.9)	216 -23.1 [-24.3, -21.9] -23.2 (-31.2,-13.9)	159 -16.2 [-17.5, -15.0] -13.5 (-24.2,-9.0)
All CSII recipients stratified by age									
Age Group	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
(-Inf,13]	59 -3.8 [-5.9, -1.7] -2.2 (-7.5,6.7)	48 -1.6 [-2.3, -1.0] -1.2 (-5.3,2.4)	20 -1.6 [-2.1, -1.0] -0.6 (-3.7,0.0)	14 -0.5 [-0.9, -0.1] -0.7 (-1.6,1.0)	2 -6.0 [-6.0, -6.0] -6.0 (-6.0,-6.0)	NA	NA	NA	NA
(13,19]	78 -6.8 [-8.4, -5.2] -7.0 (-22.0,4.5)	85 7.0 [4.9, 9.0] -0.5 (-4.3,12.5)	111 1.0 [0.5, 1.6] -0.6 (-2.8,2.8)	101 -0.2 [-1.4, 1.0] 0.0 (-1.6,4.8)	139 -7.1 [-8.4, -5.7] -5.0 (-9.8,1.5)	118 -8.5 [-10.2, -6.8] -6.9 (-12.3,1.0)	110 -7.1 [-8.6, -5.6] -3.0 (-11.9,-1.8)	57 1.8 [0.6, 3.0] 1.5 (-1.5,6.6)	32 -5.2 [-6.5, -3.9] -4.2 (-10.0,-0.2)
(19,25]	158 4.1 [3.0, 5.2] 2.5 (-5.0,12.0)	184 -0.9 [-2.1, 0.4] 0.0 (-6.2,9.0)	205 4.2 [3.5, 4.8] 2.0 (-1.0,7.0)	293 -0.7 [-1.0, -0.5] -0.2 (-2.6,2.2)	224 -4.8 [-5.5, -4.1] -1.8 (-12.6,3.0)	217 -4.3 [-5.2, -3.5] -2.2 (-7.0,1.0)	135 -1.9 [-3.1, -0.8] -2.3 (-11.2,8.0)	74 -12.5 [-15.0, -10.0] -6.0 (-32.0,1.8)	65 5.6 [3.9, 7.3] 6.0 (-2.5,12.5)
(25,45]	575 1.0 [0.5, 1.5] 1.0 (-4.2,6.0)	871 2.4 [2.1, 2.7] 2.0 (-3.6,7.0)	1,067 1.2 [1.0, 1.4] 0.1 (-1.4,2.8)	1,419 -0.3 [-0.4, -0.2] -0.3 (-2.0,1.0)	1,542 -7.3 [-7.5, -7.0] -6.5 (-11.0,-1.7)	1,452 -8.0 [-8.3, -7.7] -7.2 (-12.9,-1.7)	1,143 -5.7 [-6.0, -5.4] -5.4 (-12.0,1.0)	929 -7.2 [-7.6, -6.8] -5.0 (-14.4,0.5)	655 -6.3 [-6.7, -5.8] -4.5 (-12.2,1.2)
(45,65]	230 1.3 [0.6, 2.1] 1.0 (-4.0,6.0)	342 -0.4 [-0.8, 0.0] -0.2 (-4.0,4.5)	423 1.3 [1.1, 1.5] 0.2 (-0.3,2.5)	656 -0.3 [-0.4, -0.2] 0.0 (-1.5,0.8)	766 -5.6 [-5.9, -5.3] -4.5 (-8.9,0.0)	752 -6.6 [-6.9, -6.3] -5.0 (-11.0,-1.7)	674 -6.6 [-6.9, -6.2] -5.5 (-11.0,0.0)	585 -7.5 [-8.0, -7.1] -7.5 (-13.9,-0.5)	497 -7.5 [-7.9, -7.2] -7.0 (-12.4,-3.5)
(65, Inf]	2 7.0 [7.0, 7.0] 7.0 (7.0,7.0)	4 0.7 [-2.0, 3.3] -2.0 (-2.0,0.7)	17 2.9 [2.8, 3.1] 2.8 (2.8,2.8)	38 0.1 [0.1, 0.1] 0.0 (0.0,0.2)	42 -8.8 [-10.0, -7.6] -3.5 (-14.2,-3.2)	44 -9.0 [-9.9, -8.2] -10.3 (-15.0,-0.5)	54 -7.5 [-8.3, -6.6] -5.1 (-12.8,-5.0)	54 -7.3 [-8.2, -6.3] -8.0 (-14.0,-1.0)	29 -6.3 [-7.9, -4.6] -2.5 (-17.0,2.5)
All CSII recipients stratified by duration									
Duration	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
(-Inf,5]	185	248	249	237	176	125	63	8	2

	-2.6 [-3.6, -1.5] -2.2 (-10.8,5.7)	0.6 [-0.4, 1.6] -0.8 (-7.5,4.5)	1.4 [0.9, 2.0] -0.5 (-1.7,1.8)	0.9 [0.6, 1.1] 0.3 (-1.0,2.9)	-3.9 [-4.9, -2.9] -3.0 (-8.5,2.9)	-3.0 [-4.4, -1.5] -4.5 (-7.1,1.0)	-2.5 [-4.5, -0.5] -1.9 (-7.3,3.5)	-8.1 [-16.8, 0.7] -10.0 (-31.0,12.9)	-34.0 [-34.0, -34.0] -34.0 (-34.0,-34.0)
(5,10]	184 -0.4 [-1.3, 0.6] 1.5 (-7.2,6.2)	199 0.6 [0.0, 1.2] 1.4 (-3.8,5.0)	220 2.7 [2.2, 3.1] 0.0 (-1.3,4.1)	330 -0.2 [-0.4, 0.1] -0.3 (-2.3,2.0)	361 -6.1 [-6.6, -5.6] -5.0 (-10.0,0.8)	311 -4.0 [-4.5, -3.5] -3.0 (-8.9,0.7)	226 -0.9 [-1.6, -0.2] -1.0 (-5.4,5.3)	140 -1.0 [-2.5, 0.5] 2.6 (-4.8,9.0)	106 4.8 [3.7, 5.9] 4.3 (0.0,10.5)
(10,15]	185 2.3 [1.2, 3.4] 1.8 (-2.8,5.3)	243 5.9 [5.2, 6.6] 2.4 (-1.5,14.0)	292 3.3 [3.0, 3.7] 1.7 (-0.8,7.0)	428 -0.9 [-1.2, -0.7] -0.5 (-1.8,0.8)	427 -8.8 [-9.4, -8.3] -6.0 (-14.9,-1.8)	335 -7.3 [-7.8, -6.8] -6.3 (-12.4,-2.0)	365 -7.5 [-8.0, -7.0] -7.2 (-13.5,-2.5)	207 -8.8 [-9.7, -7.8] -7.5 (-16.5,0.8)	172 -5.5 [-6.6, -4.5] -4.5 (-11.2,1.4)
(15,20]	140 2.7 [1.7, 3.8] 1.0 (-4.0,10.9)	211 -1.2 [-2.2, -0.1] -1.0 (-5.0,4.8)	248 2.5 [2.0, 2.9] 1.2 (0.1,3.3)	376 -1.4 [-1.6, -1.2] -0.5 (-4.0,0.3)	390 -6.7 [-7.2, -6.1] -6.0 (-11.0,0.4)	399 -9.2 [-9.9, -8.6] -8.5 (-16.4,-1.0)	307 -7.3 [-8.1, -6.6] -5.0 (-14.5,1.5)	305 -8.8 [-9.5, -8.1] -6.5 (-14.4,0.5)	247 -6.8 [-7.4, -6.1] -7.8 (-12.2,-2.6)
(20, Inf]	408 1.3 [0.8, 1.8] 1.0 (-4.0,6.0)	633 1.4 [1.1, 1.7] 1.8 (-3.6,5.5)	834 0.4 [0.2, 0.5] 0.0 (-1.5,2.0)	1,150 -0.1 [-0.2, 0.0] 0.0 (-1.6,1.0)	1,361 -6.4 [-6.6, -6.2] -5.5 (-10.2,-1.2)	1,413 -7.9 [-8.2, -7.6] -7.0 (-12.0,-1.7)	1,155 -6.1 [-6.3, -5.8] -5.4 (-12.0,0.0)	1,039 -7.3 [-7.7, -7.0] -5.5 (-13.7,-1.0)	751 -7.5 [-7.9, -7.2] -5.7 (-13.2,-0.5)

$HbA1_c$ values in IFCC mmol/mol units

* IQR = interquartile range in square brackets

** 95% CI = 95% confidence interval in round brackets

Supplementary Table 3 Difference in $HbA1_c$ across time with respect to CSII initiation date stratified by DAFNE

CSII, never DAFNE. Overall									
Years since CSII	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
n	621	757	820	965	1,163	1,064	892	774	610
median[IQR]*	0.7 [0.2, 1.3]	0.5 [0.1, 0.8]	1.0 [0.8, 1.2]	-0.5 [-0.7, -0.3]	-7.4 [-7.8, -7.1]	-8.1 [-8.5, -7.7]	-5.7 [-6.1, -5.2]	-7.5 [-8.1, -7.0]	-6.1 [-6.7, -5.6]
mean(95%CI)**	0.5 (-6.4,6.5)	-0.3 (-4.0,4.9)	0.4 (-1.4,2.8)	0.0 (-2.0,1.2)	-5.5 (-12.0,-0.8)	-7.0 (-13.8,-0.7)	-5.2 (-11.5,0.4)	-5.5 (-14.4,0.5)	-5.3 (-13.8,1.7)
CSII with DAFNE Overall									
Months since CSII	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
n	481	777	1,023	1,556	1,552	1,519	1,224	925	668
median[IQR]*	0.7 [0.2, 1.3]	2.5 [2.1, 3.0]	2.0 [1.8, 2.2]	-0.3 [-0.3, -0.2]	-6.0 [-6.2, -5.8]	-6.8 [-7.0, -6.6]	-6.0 [-6.2, -5.7]	-7.0 [-7.4, -6.6]	-6.1 [-6.4, -5.8]
mean(95%CI)**	1.2 (-5.0,6.0)	3.3 (-3.7,6.5)	0.0 (-1.2,2.8)	0.0 (-1.8,1.0)	-5.0 (-10.2,-0.5)	-5.5 (-11.6,-1.5)	-5.0 (-12.5,0.1)	-5.0 (-14.0,0.5)	-5.3 (-11.4,-0.5)

$HbA1_c$ values in IFCC mmol/mol units

* IQR = interquartile range in square brackets

** 95% CI = 95% confidence interval in round brackets

Supplementary Table 4 Difference in $HbA1_c$ with respect to intervention initiation date ($HbA1_c$ in percentage units)

Difference with respect to DAFNE initiation date overall									
Years since DAFNE	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
n median[IQR]* mean(95%CI)**	2,058 -0.07 [-0.14, 0.00] -2.20 (-2.70,2.70)	2,225 0.21 [0.15, 0.27] 0.00 (-2.56,2.70)	2,775 0.28 [0.23, 0.32] 0.00 (-2.33,2.42)	4,004 -0.20 [-0.23, -0.17] 0.00 (-2.24,2.24)	3,163 -0.97 [-1.02, -0.92] -2.42 (-2.93,2.33)	2,340 -0.82 [-0.89, -0.76] -2.38 (-3.11,2.47)	1,754 -0.73 [-0.81, -0.65] -2.38 (-3.06,2.61)	1,502 -0.72 [-0.80, -0.63] -2.42 (-3.25,2.61)	1,233 -0.88 [-0.97, -0.79] -2.42 (-3.39,2.61)
Difference with respect to DAFNE initiation date by sex									
Female	1,149 -0.10 [-0.20, -0.01] -2.20 (-2.79,2.74)	1,251 0.27 [0.19, 0.36] 2.20 (-2.61,2.70)	1,541 0.23 [0.17, 0.29] 0.00 (-2.33,2.38)	2,222 -0.21 [-0.25, -0.17] 0.00 (-2.24,2.20)	1,792 -1.12 [-1.18, -1.05] -2.47 (-2.97,2.30)	1,358 -1.09 [-1.18, -1.00] -2.47 (-3.25,2.42)	1,026 -0.96 [-1.07, -0.86] -2.47 (-3.11,2.52)	882 -0.68 [-0.79, -0.56] -2.42 (-3.34,2.61)	745 -0.95 [-1.07, -0.83] -2.42 (-3.43,2.61)
Male	909 -0.03 [-0.13, 0.07] -2.20 (-2.61,2.61)	974 0.12 [0.03, 0.21] 0.00 (-2.52,2.70)	1,234 0.34 [0.27, 0.40] 0.00 (-2.29,2.42)	1,782 -0.19 [-0.24, -0.14] 0.00 (-2.29,2.24)	1,371 -0.77 [-0.85, -0.69] -2.42 (-2.84,2.42)	982 -0.45 [-0.55, -0.36] -2.24 (-2.74,2.61)	728 -0.40 [-0.52, -0.29] -2.29 (-3.00,2.61)	620 -0.78 [-0.90, -0.65] -2.42 (-3.02,2.56)	488 -0.78 [-0.93, -0.63] -2.38 (-3.34,2.52)
Difference with respect to CSII initiation date overall									
Years since CII	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
n median[IQR]* mean(95%CI)**	1,102 0.25 [0.16, 0.35] 2.24 (-2.65,2.73)	1,534 0.35 [0.27, 0.42] 2.29 (-2.52,2.70)	1,843 0.45 [0.39, 0.50] 2.17 (-2.27,2.41)	2,521 -0.28 [-0.32, -0.23] 0.00 (-2.31,2.24)	2,715 -1.76 [-1.81, -1.72] -2.65 (-3.14,-2.20)	2,583 -1.91 [-1.96, -1.87] -2.76 (-3.25,-2.24)	2,116 -1.55 [-1.61, -1.49] -2.62 (-3.25,2.18)	1,699 -1.66 [-1.72, -1.59] -2.65 (-3.46,2.20)	1,278 -1.56 [-1.64, -1.49] -2.64 (-3.27,2.18)
Difference with respect to CSII initiation date by sex									
Female	695 0.08 [-0.04, 0.20] 2.24 (-2.79,2.70)	1,012 0.35 [0.25, 0.44] 2.33 (-2.52,2.65)	1,142 0.37 [0.30, 0.44] 2.16 (-2.29,2.41)	1,474 -0.10 [-0.16, -0.04] 0.00 (-2.30,2.28)	1,709 -1.96 [-2.02, -1.91] -2.74 (-3.20,-2.29)	1,659 -2.03 [-2.09, -1.97] -2.79 (-3.35,-2.30)	1,379 -1.58 [-1.65, -1.51] -2.61 (-3.34,2.18)	1,128 -1.68 [-1.77, -1.60] -2.67 (-3.61,2.20)	881 -1.73 [-1.82, -1.64] -2.70 (-3.39,-2.17)
Male	407 0.55 [0.41, 0.69] 2.24 (-2.47,2.79)	522 0.35 [0.23, 0.47] 2.24 (-2.52,2.74)	701 0.57 [0.48, 0.66] 2.22 (-2.24,2.42)	1,047 -0.54 [-0.60, -0.47] -2.20 (-2.33,2.20)	1,006 -1.42 [-1.50, -1.34] -2.52 (-3.06,2.28)	924 -1.70 [-1.78, -1.62] -2.61 (-3.16,-2.20)	737 -1.48 [-1.58, -1.39] -2.63 (-3.03,0.00)	571 -1.61 [-1.71, -1.50] -2.61 (-3.17,0.00)	397 -1.19 [-1.32, -1.06] -2.52 (-2.93,2.18)

$HbA1_c$ values in DCCT percentage units

* IQR = interquartile range in square brackets

** 95% CI = 95% confidence interval in round brackets

Supplementary Table 5 Difference in $HbA1_c$ over time with respect to DAFNE initiation date ($HbA1_c$ percentage units)

All DAFNE recipients									
Years since DAFNE	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
n median[IQR]* mean(95%CI)**	2,058 -0.07 [-0.14, 0.00] -2.20 (-2.70,2.70)	2,225 0.21 [0.15, 0.27] 0.00 (-2.56,2.70)	2,775 0.28 [0.23, 0.32] 0.00 (-2.33,2.42)	4,004 -0.20 [-0.23, -0.17] 0.00 (-2.24,2.24)	3,163 -0.97 [-1.02, -0.92] -2.42 (-2.93,2.33)	2,340 -0.82 [-0.89, -0.76] -2.38 (-3.11,2.47)	1,754 -0.73 [-0.81, -0.65] -2.38 (-3.06,2.61)	1,502 -0.72 [-0.80, -0.63] -2.42 (-3.25,2.61)	1,233 -0.88 [-0.97, -0.79] -2.42 (-3.39,2.61)
All DAFNE recipients stratified by $HbA1_c$									
$HbA1_c$	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
(-Inf,53]	154 1.60 [1.38, 1.83] 2.65 (-2.20,3.20)	211 1.48 [1.30, 1.67] 2.52 (-2.20,2.84)	337 0.52 [0.38, 0.66] 0.00 (-2.29,2.42)	479 -0.12 [-0.21, -0.03] 0.00 (-2.24,2.20)	334 1.34 [1.22, 1.46] 2.42 (0.00,2.70)	236 1.12 [0.95, 1.29] 2.38 (-2.29,2.88)	158 2.00 [1.79, 2.21] 2.70 (2.24,4.12)	122 2.13 [1.91, 2.35] 3.02 (2.37,3.61)	88 2.37 [2.13, 2.62] 3.34 (2.52,3.61)
(53,58]	220 0.89 [0.69, 1.08] 2.31 (-2.33,2.76)	255 1.08 [0.91, 1.26] 2.33 (-2.29,2.86)	285 0.66 [0.52, 0.79] 2.20 (-2.24,2.52)	479 -0.46 [-0.55, -0.38] 0.00 (-2.24,0.00)	311 0.29 [0.14, 0.43] 2.24 (-2.52,2.61)	268 1.15 [1.00, 1.31] 2.33 (-2.24,2.69)	188 0.37 [0.17, 0.57] 2.20 (-2.42,2.65)	159 0.48 [0.26, 0.69] 2.33 (-2.52,2.61)	116 0.22 [-0.03, 0.47] 2.33 (-2.42,2.65)
(58,75]	943 0.15 [0.06, 0.25] 0.00 (-2.61,2.61)	1,048 0.36 [0.27, 0.44] 2.24 (-2.47,2.70)	1,317 0.21 [0.15, 0.27] 0.00 (-2.29,2.38)	1,863 -0.13 [-0.18, -0.09] 0.00 (-2.24,2.24)	1,516 -0.87 [-0.94, -0.81] -2.40 (-2.79,2.29)	1,047 -0.64 [-0.73, -0.55] -2.33 (-2.79,2.42)	749 -0.19 [-0.30, -0.08] -2.29 (-2.70,2.70)	623 -0.19 [-0.31, -0.07] -2.24 (-2.70,2.65)	544 -0.20 [-0.33, -0.07] -2.29 (-2.79,2.56)
(75,85]	411 -0.51 [-0.66, -0.36] -2.33 (-2.70,2.61)	392 -0.12 [-0.27, 0.03] -2.22 (-2.70,2.74)	474 0.29 [0.17, 0.40] 0.00 (-2.33,2.33)	731 -0.25 [-0.32, -0.17] 0.00 (-2.29,2.20)	551 -1.70 [-1.81, -1.59] -2.70 (-3.32,-2.29)	454 -1.72 [-1.84, -1.59] -2.93 (-3.48,0.00)	348 -1.93 [-2.07, -1.80] -2.97 (-3.80,-2.24)	246 -1.52 [-1.70, -1.34] -2.88 (-3.34,2.24)	208 -1.46 [-1.65, -1.26] -2.79 (-3.43,2.26)
(85, Inf]	330 -1.57 [-1.77, -1.38] -2.84 (-3.71,2.49)	319 -1.41 [-1.57, -1.26] -2.52 (-3.11,2.24)	362 -0.01 [-0.15, 0.13] 0.00 (-2.56,2.47)	452 -0.21 [-0.33, -0.10] 0.00 (-2.42,2.29)	451 -2.96 [-3.09, -2.82] -3.34 (-4.80,-2.72)	335 -3.13 [-3.30, -2.97] -3.71 (-4.99,-2.70)	311 -2.75 [-2.93, -2.57] -3.25 (-4.85,-2.36)	352 -2.62 [-2.78, -2.46] -3.52 (-4.53,-2.33)	277 -3.28 [-3.46, -3.11] -3.80 (-4.71,-2.70)
All DAFNE recipients stratified by age									
Age group	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
(13,19]	372 -0.67 [-0.85, -0.50] -2.49 (-3.16,2.70)	278 0.14 [-0.06, 0.34] 1.10 (-2.88,2.72)	202 0.20 [-0.01, 0.41] 0.00 (-2.42,2.42)	151 0.43 [0.25, 0.62] 0.00 (-2.20,2.33)	72 0.99 [0.66, 1.33] 2.52 (-2.49,3.24)	9 1.56 [0.27, 2.86] 2.52 (-2.56,4.89)	NA	NA	NA
(19,25]	244 0.79 [0.55, 1.03] 2.31 (-2.54,3.09)	290 0.65 [0.46, 0.85] 2.47 (-2.70,2.97)	421 0.33 [0.20, 0.46] 0.00 (-2.42,2.52)	676 -0.50 [-0.58, -0.43] 0.00 (-2.33,0.00)	460 -0.61 [-0.78, -0.45] -2.38 (-2.88,2.79)	321 -0.33 [-0.53, -0.12] -2.24 (-3.02,2.97)	221 -0.78 [-1.01, -0.55] -2.33 (-3.06,2.74)	184 -1.07 [-1.35, -0.78] -2.42 (-4.44,2.70)	112 0.22 [-0.14, 0.58] 2.33 (-3.84,3.34)
(25,45]	839 -0.10 [-0.20, 0.00] -2.20 (-2.70,2.61)	918 0.11 [0.01, 0.20] 0.00 (-2.52,2.65)	1,264 0.16 [0.10, 0.23] 0.00 (-2.29,2.38)	1,848 -0.14 [-0.19, -0.09] 0.00 (-2.24,2.24)	1,514 -1.09 [-1.16, -1.02] -2.52 (-3.06,2.33)	1,165 -1.00 [-1.10, -0.91] -2.42 (-3.25,2.42)	847 -1.07 [-1.18, -0.96] -2.52 (-3.25,2.61)	718 -0.87 [-0.99, -0.76] -2.56 (-3.25,2.56)	564 -1.53 [-1.66, -1.39] -2.79 (-3.52,2.42)
(45,65]	556 -0.14 [-0.27, -0.01] -2.20 (-2.65,2.61)	671 0.10 [-0.01, 0.20] 0.00 (-2.52,2.61)	789 0.38 [0.30, 0.47] 0.00 (-2.33,2.42)	1,146 -0.14 [-0.20, -0.08] 0.00 (-2.24,2.24)	926 -1.13 [-1.21, -1.04] -2.42 (-2.79,2.24)	698 -0.69 [-0.80, -0.59] -2.33 (-2.88,2.38)	560 -0.28 [-0.40, -0.15] -2.24 (-2.79,2.61)	480 -0.37 [-0.50, -0.23] -2.33 (-2.93,2.79)	457 -0.42 [-0.56, -0.28] -2.33 (-2.84,2.61)
(65, Inf]	47 1.71 [1.37, 2.05] 2.47 (2.24,2.70)	68 1.06 [0.76, 1.37] 2.38 (-2.20,2.84)	99 0.81 [0.62, 1.01] 2.20 (0.00,2.38)	183 -0.63 [-0.77, -0.48] 0.00 (-2.33,0.00)	191 -0.79 [-0.96, -0.62] -2.33 (-2.65,2.24)	147 -1.25 [-1.45, -1.04] -2.42 (-2.74,2.24)	126 -0.37 [-0.64, -0.10] -2.24 (-2.66,2.33)	120 -0.65 [-0.93, -0.37] -2.29 (-2.88,2.61)	100 -0.62 [-0.93, -0.31] -2.36 (-3.25,2.45)
All DAFNE recipients stratified by duration									
Duration	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
(-Inf,5]	468 -0.24 [-0.41, -0.07] -2.33 (-2.93,2.74)	512 0.03 [-0.12, 0.18] -2.20 (-2.94,2.88)	713 0.44 [0.33, 0.54] 0.00 (-2.33,2.42)	927 -0.07 [-0.13, 0.00] 0.00 (-2.20,2.24)	605 0.12 [-0.01, 0.25] 2.20 (-2.56,2.88)	387 0.91 [0.73, 1.08] 2.47 (-2.36,3.34)	204 0.79 [0.54, 1.04] 2.33 (-2.62,3.42)	94 0.03 [-0.35, 0.41] 1.17 (-2.82,3.25)	10 -0.80 [-2.31, 0.71] -3.98 (-3.98,4.62)
(5,10]	389	408	501	665	463	359	278	269	249

	0.16 [-0.02, 0.33] 2.24 (-2.79,2.84)	0.45 [0.30, 0.60] 2.29 (-2.52,2.74)	0.23 [0.13, 0.34] 0.00 (-2.33,2.42)	-0.32 [-0.40, -0.23] 0.00 (-2.29,2.20)	-0.73 [-0.86, -0.59] -2.38 (-2.79,2.33)	-0.43 [-0.59, -0.27] -2.24 (-2.81,2.56)	-0.64 [-0.85, -0.44] -2.33 (-3.20,2.87)	0.28 [0.07, 0.49] 2.33 (-2.88,3.11)	-0.27 [-0.48, -0.06] -2.24 (-2.97,2.74)
(10,15]	327 -0.53 [-0.70, -0.37] -2.33 (-2.88,2.52)	315 0.00 [-0.17, 0.17] -2.24 (-2.65,2.65)	339 0.07 [-0.06, 0.20] 0.00 (-2.33,2.47)	536 -0.13 [-0.22, -0.05] 0.00 (-2.29,2.24)	439 -1.62 [-1.75, -1.49] -2.61 (-3.20,2.24)	338 -1.66 [-1.82, -1.50] -2.70 (-3.77,2.37)	254 -1.44 [-1.62, -1.27] -2.47 (-3.16,2.20)	286 -1.24 [-1.42, -1.06] -2.56 (-3.34,2.38)	204 -1.62 [-1.83, -1.41] -3.02 (-3.52,2.33)
(15,20]	303 0.12 [-0.04, 0.29] 0.00 (-2.52,2.61)	332 0.68 [0.53, 0.83] 2.24 (-2.39,2.84)	406 0.00 [-0.12, 0.12] 0.00 (-2.29,2.33)	570 -0.13 [-0.22, -0.05] 0.00 (-2.29,2.24)	511 -1.25 [-1.38, -1.13] -2.52 (-2.97,2.24)	368 -1.32 [-1.49, -1.16] -2.61 (-3.43,2.33)	230 -1.79 [-1.98, -1.60] -2.72 (-3.43,2.24)	190 -1.74 [-1.96, -1.53] -2.74 (-4.53,2.33)	143 -1.16 [-1.44, -0.88] -2.65 (-3.29,2.61)
(20, Inf]	571 0.08 [-0.04, 0.19] 0.00 (-2.52,2.61)	658 0.07 [-0.04, 0.17] 0.00 (-2.42,2.55)	816 0.39 [0.32, 0.47] 0.00 (-2.29,2.42)	1,306 -0.29 [-0.35, -0.24] 0.00 (-2.24,2.20)	1,145 -1.26 [-1.34, -1.18] -2.52 (-3.02,2.20)	888 -1.21 [-1.30, -1.12] -2.47 (-3.06,2.24)	788 -0.62 [-0.72, -0.51] -2.38 (-2.97,2.52)	663 -0.71 [-0.83, -0.59] -2.42 (-3.16,2.61)	627 -0.82 [-0.95, -0.70] -2.38 (-3.36,2.52)

$HbA1_c$ values in DCCT percentage units

* IQR = interquartile range in square brackets

** 95% CI = 95% confidence interval in round brackets

Supplementary Table 6 Difference in $HbA1_c$ across time with respect to CSII initiation date by strata ($HbA1_c$ in percentage units)

All CSII recipients									
Years since CII	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
n median[IQR]* mean(95%CI)**	1,102 0.25 [0.16, 0.35] 2.24 (-2.65,2.73)	1,534 0.35 [0.27, 0.42] 2.29 (-2.52,2.70)	1,843 0.45 [0.39, 0.50] 2.17 (-2.27,2.41)	2,521 -0.28 [-0.32, -0.23] 0.00 (-2.31,2.24)	2,715 -1.76 [-1.81, -1.72] -2.65 (-3.14,-2.20)	2,583 -1.91 [-1.96, -1.87] -2.76 (-3.25,-2.24)	2,116 -1.55 [-1.61, -1.49] -2.62 (-3.25,2.18)	1,699 -1.66 [-1.72, -1.59] -2.65 (-3.46,2.20)	1,278 -1.56 [-1.64, -1.49] -2.64 (-3.27,2.18)
All CSII recipients stratified by $HbA1_c$									
$HbA1_c$	**-48 to -36**	**-36 to -24**	**-24 to -12**	**-12 to 0**	**0 to 12**	**12 to 24**	**24 to 36**	**36 to 48**	**48 to 60**
(-Inf,53]	126 0.94 [0.71, 1.18] 2.24 (-2.31,2.90)	217 2.04 [1.86, 2.21] 2.74 (2.24,3.05)	221 -0.25 [-0.43, -0.08] -2.21 (-2.50,2.38)	291 0.13 [0.01, 0.25] 0.00 (-2.21,2.24)	293 0.41 [0.26, 0.56] 2.22 (-2.47,2.72)	286 0.18 [0.03, 0.33] 2.17 (-2.33,2.38)	206 0.30 [0.12, 0.49] 2.31 (-2.52,2.55)	187 -0.12 [-0.32, 0.08] -2.20 (-2.42,2.73)	140 0.40 [0.18, 0.61] 2.28 (-2.45,2.52)
(53,58]	100 2.59 [2.41, 2.77] 2.64 (2.35,3.40)	104 1.40 [1.16, 1.64] 2.71 (-2.24,3.23)	228 0.73 [0.57, 0.90] 2.16 (-2.20,2.47)	261 -0.35 [-0.49, -0.22] -2.18 (-2.38,2.19)	282 -0.78 [-0.93, -0.63] -2.36 (-2.61,2.35)	214 -1.24 [-1.40, -1.08] -2.42 (-2.70,0.00)	190 -0.56 [-0.76, -0.37] -2.33 (-2.79,2.35)	143 -0.88 [-1.10, -0.65] -2.33 (-3.13,2.22)	96 0.77 [0.50, 1.04] 2.35 (-2.44,2.51)
(58,75]	590 0.33 [0.21, 0.45] 2.26 (-2.52,2.72)	868 0.25 [0.15, 0.34] 2.24 (-2.48,2.56)	1,004 0.35 [0.28, 0.42] 2.16 (-2.24,2.38)	1,462 -0.24 [-0.29, -0.18] 0.00 (-2.29,2.27)	1,557 -1.71 [-1.76, -1.65] -2.61 (-3.02,-2.21)	1,464 -1.96 [-2.02, -1.90] -2.79 (-3.23,-2.30)	1,147 -1.39 [-1.46, -1.32] -2.56 (-3.02,2.24)	930 -1.42 [-1.51, -1.34] -2.60 (-3.16,2.24)	687 -1.69 [-1.78, -1.59] -2.70 (-3.28,0.00)
(75,85]	151 -0.41 [-0.66, -0.17] -2.27 (-2.77,2.47)	176 0.10 [-0.10, 0.31] 2.31 (-2.47,2.60)	185 0.81 [0.65, 0.98] 2.30 (-2.24,2.45)	292 -0.21 [-0.35, -0.07] 0.00 (-2.36,2.36)	299 -2.98 [-3.06, -2.90] -3.14 (-3.68,-2.58)	350 -2.64 [-2.73, -2.55] -3.02 (-3.39,-2.35)	341 -2.72 [-2.81, -2.63] -3.11 (-3.52,-2.56)	223 -2.45 [-2.61, -2.28] -3.16 (-3.71,-2.65)	196 -2.31 [-2.46, -2.15] -2.67 (-3.20,-2.61)
(85, Inf]	135 -1.70 [-1.99, -1.40] -3.22 (-4.16,2.38)	169 -1.68 [-1.94, -1.43] -3.22 (-3.84,2.29)	205 1.02 [0.85, 1.19] 2.30 (-2.28,2.64)	215 -1.13 [-1.30, -0.96] -2.39 (-2.65,2.20)	284 -4.03 [-4.13, -3.92] -4.10 (-4.63,-3.54)	269 -3.49 [-3.65, -3.33] -3.92 (-4.89,-3.11)	232 -3.05 [-3.24, -2.87] -4.00 (-4.64,-2.97)	216 -3.71 [-3.90, -3.51] -4.28 (-5.01,-3.42)	159 -3.23 [-3.42, -3.04] -3.39 (-4.36,-2.97)
All CSII recipients stratified by age									

Age Group	-4	-3	-2	-1	0	1	2	3	4
(-Inf,13]	59 -0.53 [-0.96, -0.09] -2.36 (-2.84,2.76)	48 -0.78 [-1.13, -0.43] -2.26 (-2.64,2.37)	20 -1.22 [-1.65, -0.78] -2.21 (-2.49,0.00)	14 -0.05 [-0.68, 0.58] -0.06 (-2.29,2.25)	2 -2.70 [-2.70, -2.70] -2.70 (-2.70,-2.70)	NA	NA	NA	NA
(13,19]	78 -1.23 [-1.60, -0.87] -2.79 (-4.16,2.56)	85 0.41 [0.02, 0.80] -2.20 (-2.55,3.29)	111 0.00 [-0.25, 0.24] -2.21 (-2.40,2.40)	101 0.11 [-0.17, 0.39] 0.00 (-2.29,2.58)	139 -1.50 [-1.76, -1.24] -2.61 (-3.04,2.29)	118 -1.25 [-1.57, -0.93] -2.78 (-3.28,2.24)	110 -2.13 [-2.39, -1.88] -2.42 (-3.24,-2.31)	57 1.03 [0.68, 1.38] 2.29 (-2.29,2.75)	32 -1.82 [-2.20, -1.43] -2.54 (-3.06,-2.17)
(19,25]	158 0.94 [0.70, 1.19] 2.38 (-2.61,3.25)	184 -0.09 [-0.34, 0.16] 0.00 (-2.72,2.98)	205 1.13 [0.95, 1.30] 2.33 (-2.24,2.79)	293 -0.30 [-0.44, -0.17] -2.17 (-2.39,2.35)	224 -0.88 [-1.08, -0.69] -2.31 (-3.30,2.42)	217 -1.02 [-1.22, -0.82] -2.35 (-2.79,2.24)	135 -0.58 [-0.85, -0.30] -2.36 (-3.17,2.88)	74 -1.61 [-2.05, -1.16] -2.70 (-5.08,2.31)	65 1.21 [0.82, 1.59] 2.70 (-2.38,3.29)
(25,45]	575 0.32 [0.20, 0.45] 2.24 (-2.53,2.70)	871 0.67 [0.57, 0.77] 2.33 (-2.48,2.79)	1,067 0.28 [0.21, 0.35] 2.16 (-2.28,2.41)	1,419 -0.33 [-0.39, -0.27] -2.18 (-2.33,2.24)	1,542 -1.98 [-2.04, -1.92] -2.74 (-3.16,-2.30)	1,452 -2.09 [-2.15, -2.03] -2.81 (-3.33,-2.30)	1,143 -1.51 [-1.59, -1.43] -2.65 (-3.25,2.24)	929 -1.64 [-1.74, -1.55] -2.61 (-3.46,2.20)	655 -1.38 [-1.49, -1.27] -2.56 (-3.27,2.26)
(45,65]	230 0.29 [0.10, 0.48] 2.24 (-2.52,2.70)	342 -0.07 [-0.22, 0.07] -2.17 (-2.52,2.56)	423 0.66 [0.55, 0.76] 2.17 (-2.18,2.38)	656 -0.28 [-0.37, -0.20] 0.00 (-2.29,2.22)	766 -1.56 [-1.65, -1.47] -2.56 (-2.96,0.00)	752 -1.89 [-1.98, -1.81] -2.61 (-3.16,-2.30)	674 -1.65 [-1.75, -1.56] -2.65 (-3.16,0.00)	585 -1.92 [-2.02, -1.81] -2.84 (-3.42,-2.20)	497 -2.16 [-2.25, -2.06] -2.79 (-3.28,-2.47)
(65, Inf]	2 2.79 [2.79, 2.79] 2.79 (2.79,2.79)	4 -1.02 [-2.33, 0.30] -2.33 (-2.33,-1.02)	17 2.42 [2.40, 2.44] 2.40 (2.40,2.40)	38 0.58 [0.42, 0.73] 0.00 (0.00,1.63)	42 -2.95 [-3.06, -2.85] -2.47 (-3.45,-2.45)	44 -2.78 [-2.93, -2.63] -3.10 (-3.52,-2.20)	54 -2.36 [-2.61, -2.11] -2.62 (-3.32,-2.61)	54 -2.02 [-2.29, -1.75] -2.88 (-3.43,-2.24)	29 -1.39 [-1.87, -0.91] -2.38 (-3.71,2.38)
All CSII recipients stratified by duration									
Duration	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
(-Inf,5]	185 -0.83 [-1.06, -0.59] -2.36 (-3.13,2.67)	248 -0.03 [-0.24, 0.17] -2.22 (-2.84,2.56)	249 -0.34 [-0.51, -0.18] -2.20 (-2.30,2.31)	237 0.44 [0.29, 0.59] 2.18 (-2.24,2.42)	176 -0.94 [-1.16, -0.72] -2.42 (-2.93,2.42)	125 -0.46 [-0.75, -0.17] -2.56 (-2.80,2.24)	63 -0.53 [-0.95, -0.12] -2.32 (-2.82,2.47)	8 -0.74 [-2.35, 0.87] -0.91 (-4.99,3.33)	2 -5.26 [-5.26, -5.26] -5.26 (-5.26,-5.26)
(5,10]	184 0.25 [0.02, 0.48] 2.29 (-2.81,2.72)	199 0.28 [0.08, 0.48] 2.28 (-2.49,2.61)	220 0.35 [0.18, 0.52] 0.00 (-2.27,2.52)	330 -0.43 [-0.56, -0.31] -2.18 (-2.36,2.33)	361 -1.47 [-1.61, -1.33] -2.61 (-3.06,2.22)	311 -1.11 [-1.26, -0.96] -2.42 (-2.96,2.21)	226 -0.29 [-0.48, -0.10] -2.24 (-2.64,2.64)	140 0.68 [0.39, 0.96] 2.39 (-2.58,2.97)	106 1.49 [1.24, 1.74] 2.55 (0.00,3.11)
(10,15]	185 0.95 [0.73, 1.17] 2.31 (-2.40,2.64)	243 1.22 [1.04, 1.40] 2.37 (-2.29,3.43)	292 0.99 [0.85, 1.13] 2.30 (-2.22,2.79)	428 -0.46 [-0.57, -0.35] -2.20 (-2.31,2.22)	427 -2.20 [-2.32, -2.09] -2.70 (-3.51,-2.31)	335 -2.07 [-2.18, -1.95] -2.73 (-3.29,-2.33)	365 -2.12 [-2.24, -2.00] -2.81 (-3.39,-2.38)	207 -1.79 [-1.99, -1.59] -2.84 (-3.66,2.22)	172 -1.38 [-1.60, -1.16] -2.56 (-3.18,2.28)
(15,20]	140 0.57 [0.32, 0.83] 2.24 (-2.52,3.15)	211 -0.28 [-0.50, -0.05] -2.24 (-2.61,2.58)	248 1.56 [1.44, 1.68] 2.26 (2.16,2.45)	376 -0.62 [-0.73, -0.51] -2.20 (-2.52,2.18)	390 -1.64 [-1.77, -1.50] -2.70 (-3.16,2.19)	399 -2.11 [-2.24, -1.98] -2.93 (-3.65,-2.24)	307 -1.64 [-1.81, -1.48] -2.61 (-3.48,2.29)	305 -1.84 [-2.00, -1.68] -2.74 (-3.46,2.20)	247 -2.00 [-2.16, -1.85] -2.87 (-3.27,-2.39)
(20, Inf]	408 0.32 [0.18, 0.47] 2.24 (-2.52,2.70)	633 0.39 [0.29, 0.50] 2.32 (-2.48,2.65)	834 0.19 [0.11, 0.27] 0.00 (-2.29,2.33)	1,150 -0.21 [-0.27, -0.14] 0.00 (-2.29,2.24)	1,361 -1.85 [-1.91, -1.79] -2.65 (-3.08,-2.26)	1,413 -2.13 [-2.19, -2.07] -2.79 (-3.25,-2.30)	1,155 -1.64 [-1.72, -1.57] -2.65 (-3.25,0.00)	1,039 -1.90 [-1.98, -1.82] -2.65 (-3.40,-2.24)	751 -1.88 [-1.97, -1.79] -2.67 (-3.36,-2.20)

HbA1$_c$ values in DCCT percentage units

* IQR = interquartile range in square brackets

** 95% CI = 95% confidence interval in round brackets

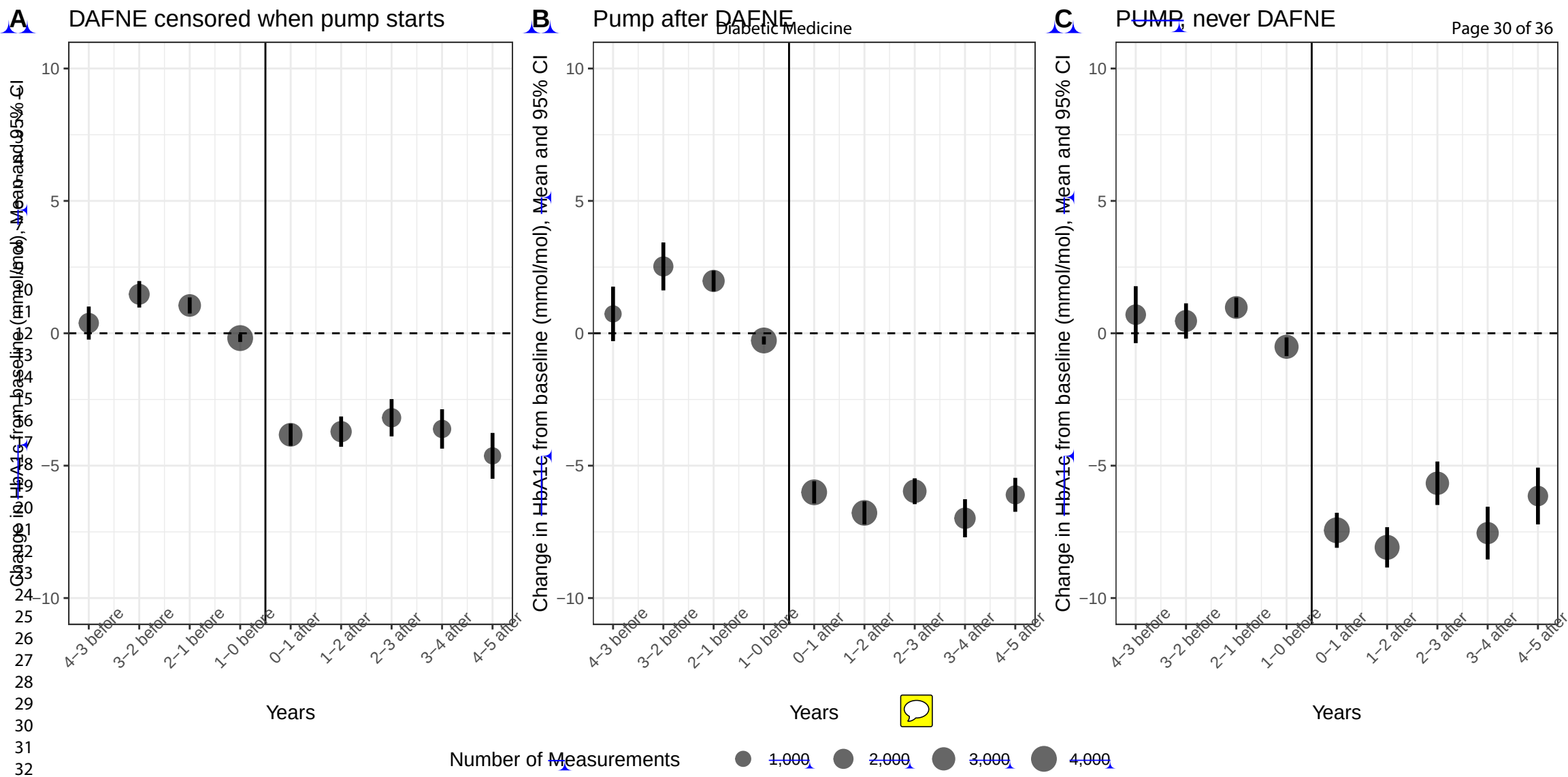
Supplementary Table 7 Difference in HbA1$_c$ across time with respect to CSII initiation date stratified by DAFNE (HbA1$_c$ in percentage units)

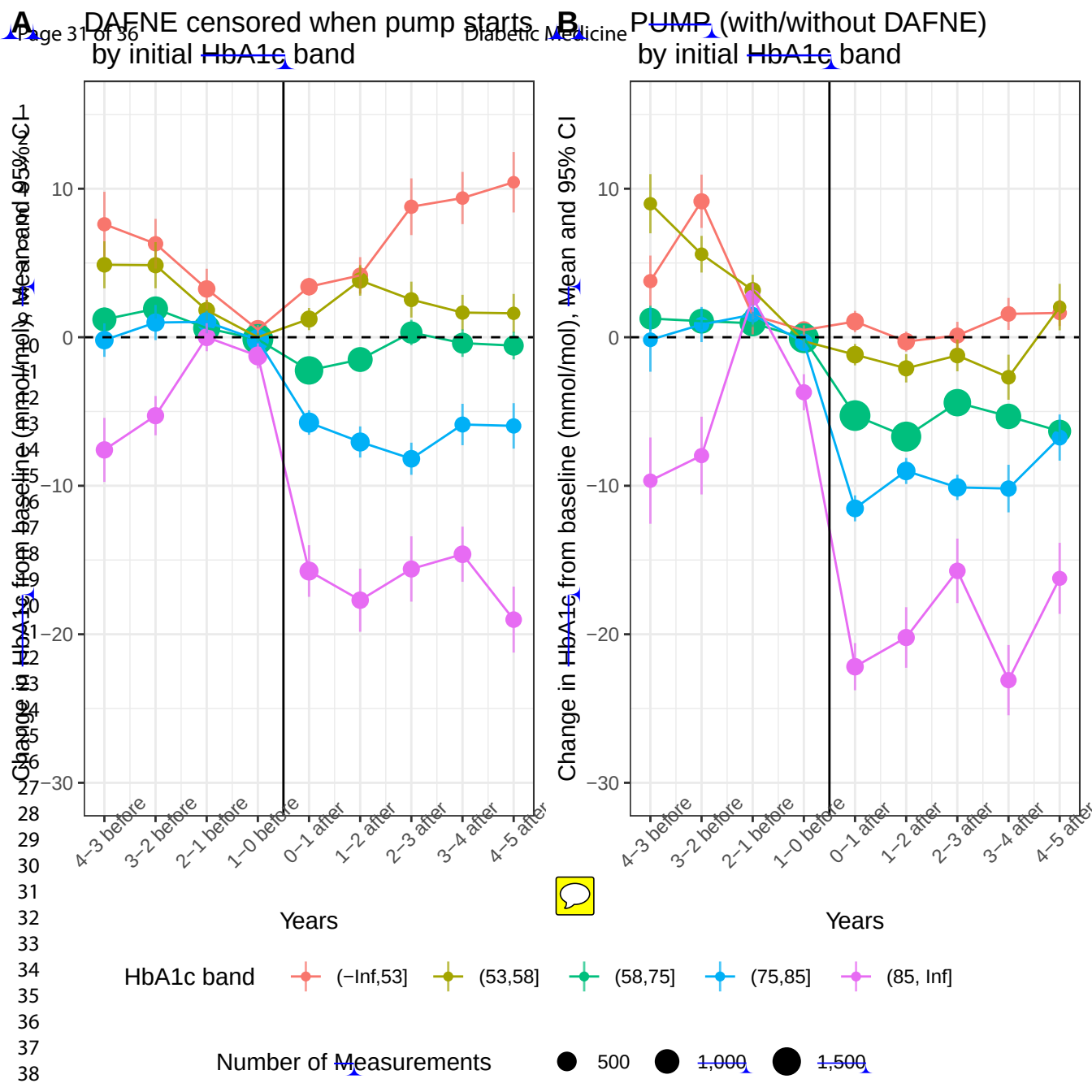
CSII, never DAFNE. Overall									
Years since CSII	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
n median[IQR]* mean(95%CI)**	621 0.19 [0.07, 0.32] 2.20 (-2.74,2.74)	757 -0.02 [-0.12, 0.09] -2.18 (-2.52,2.60)	820 0.56 [0.48, 0.64] 2.18 (-2.28,2.40)	965 -0.30 [-0.37, -0.22] 0.00 (-2.33,2.26)	1,163 -1.83 [-1.91, -1.76] -2.65 (-3.25,-2.22)	1,064 -1.96 [-2.04, -1.88] -2.79 (-3.41,-2.21)	892 -1.53 [-1.62, -1.43] -2.62 (-3.20,2.18)	774 -1.67 [-1.78, -1.57] -2.65 (-3.46,2.20)	610 -1.43 [-1.55, -1.31] -2.64 (-3.41,2.30)
CSII with DAFNE Overall									
Months since CSII	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
n median[IQR]* mean(95%CI)**	481 0.34 [0.20, 0.47] 2.26 (-2.61,2.70)	777 0.70 [0.60, 0.81] 2.45 (-2.49,2.74)	1,023 0.36 [0.28, 0.43] 0.00 (-2.26,2.41)	1,556 -0.27 [-0.32, -0.21] 0.00 (-2.31,2.24)	1,552 -1.71 [-1.77, -1.65] -2.61 (-3.09,-2.20)	1,519 -1.88 [-1.94, -1.83] -2.65 (-3.21,-2.29)	1,224 -1.56 [-1.64, -1.49] -2.61 (-3.29,2.16)	925 -1.64 [-1.73, -1.56] -2.61 (-3.43,2.20)	668 -1.68 [-1.77, -1.59] -2.64 (-3.20,-2.20)

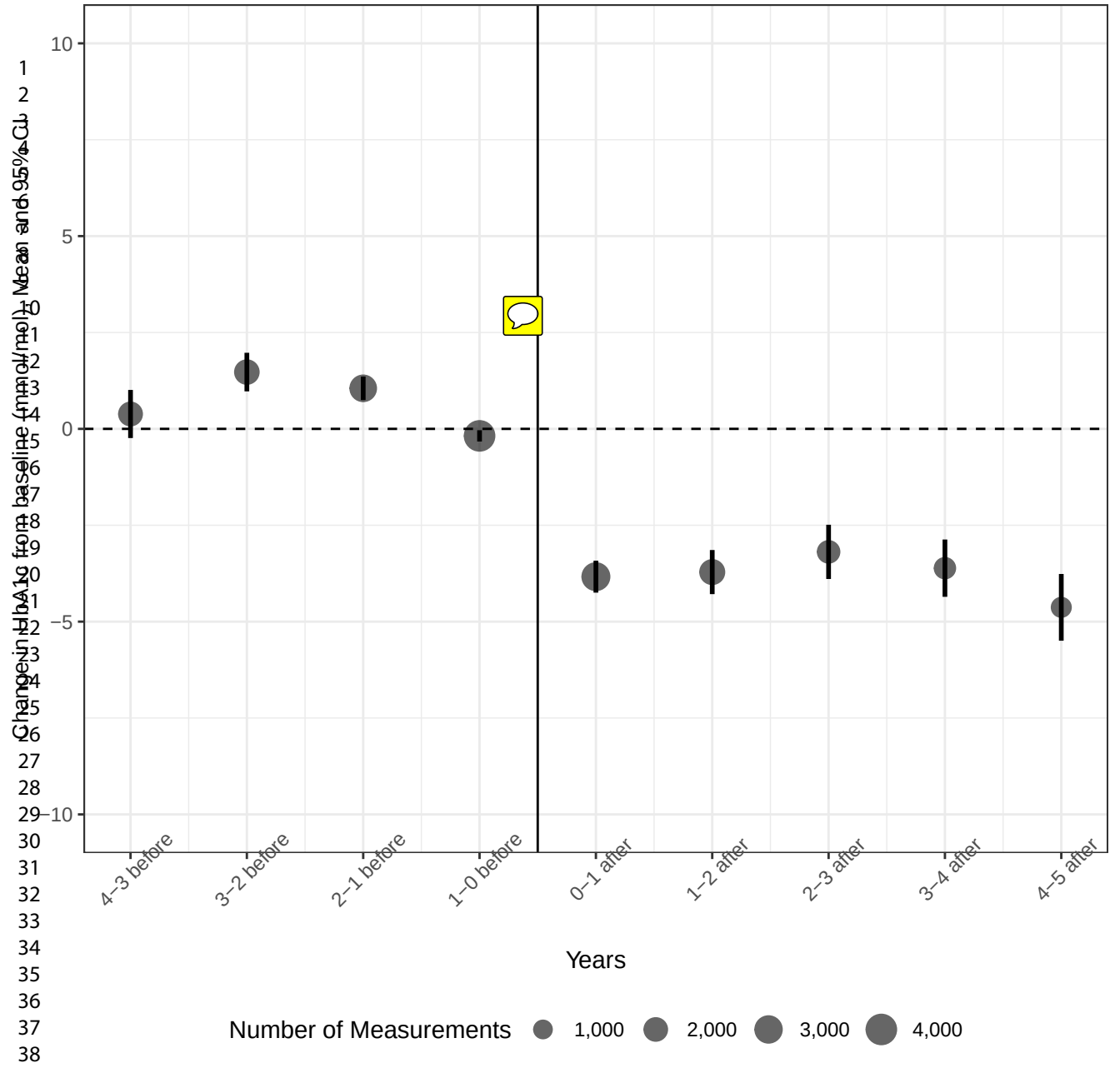
HbA1$_c$ values in DCCT percentage units

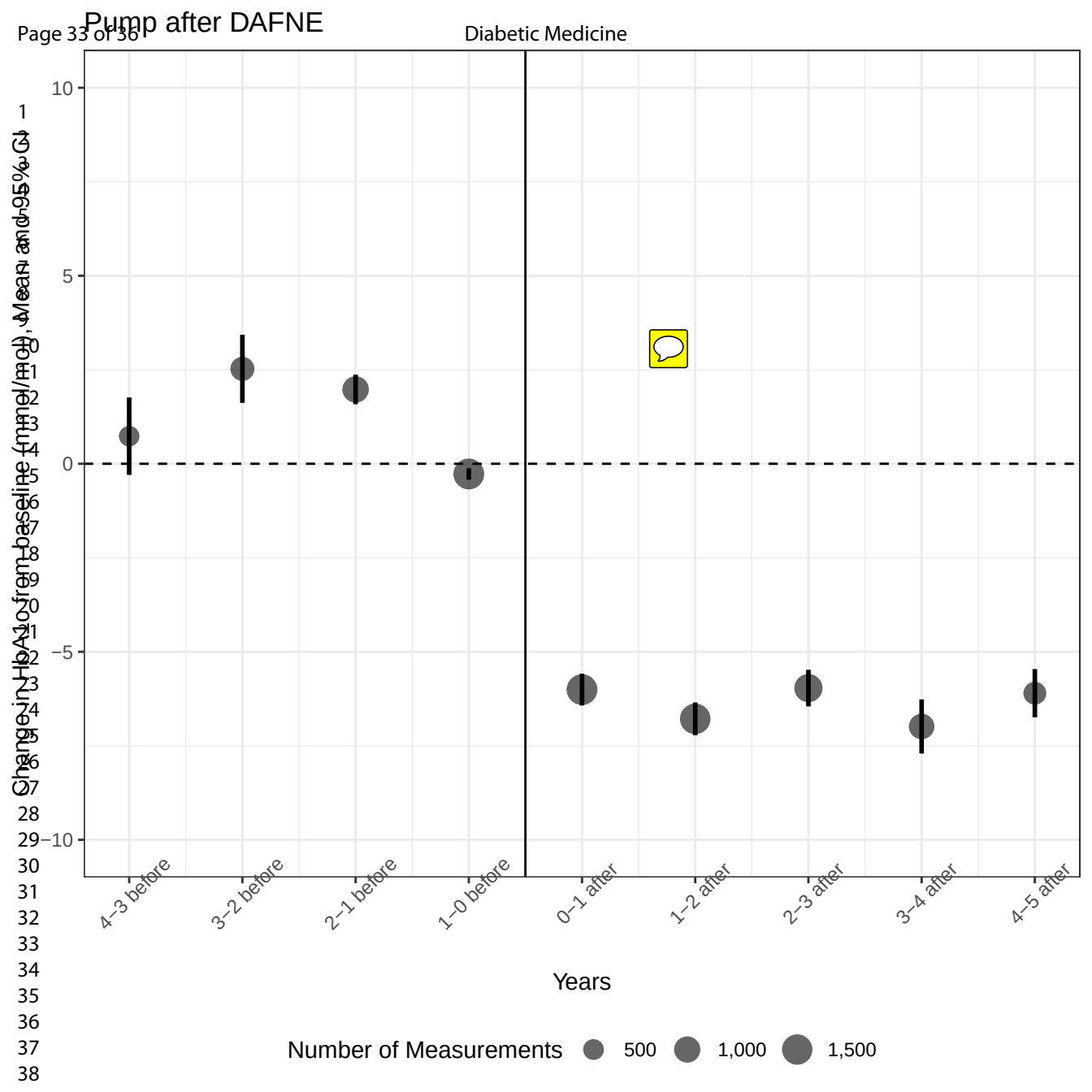
* IQR = interquartile range in square brackets

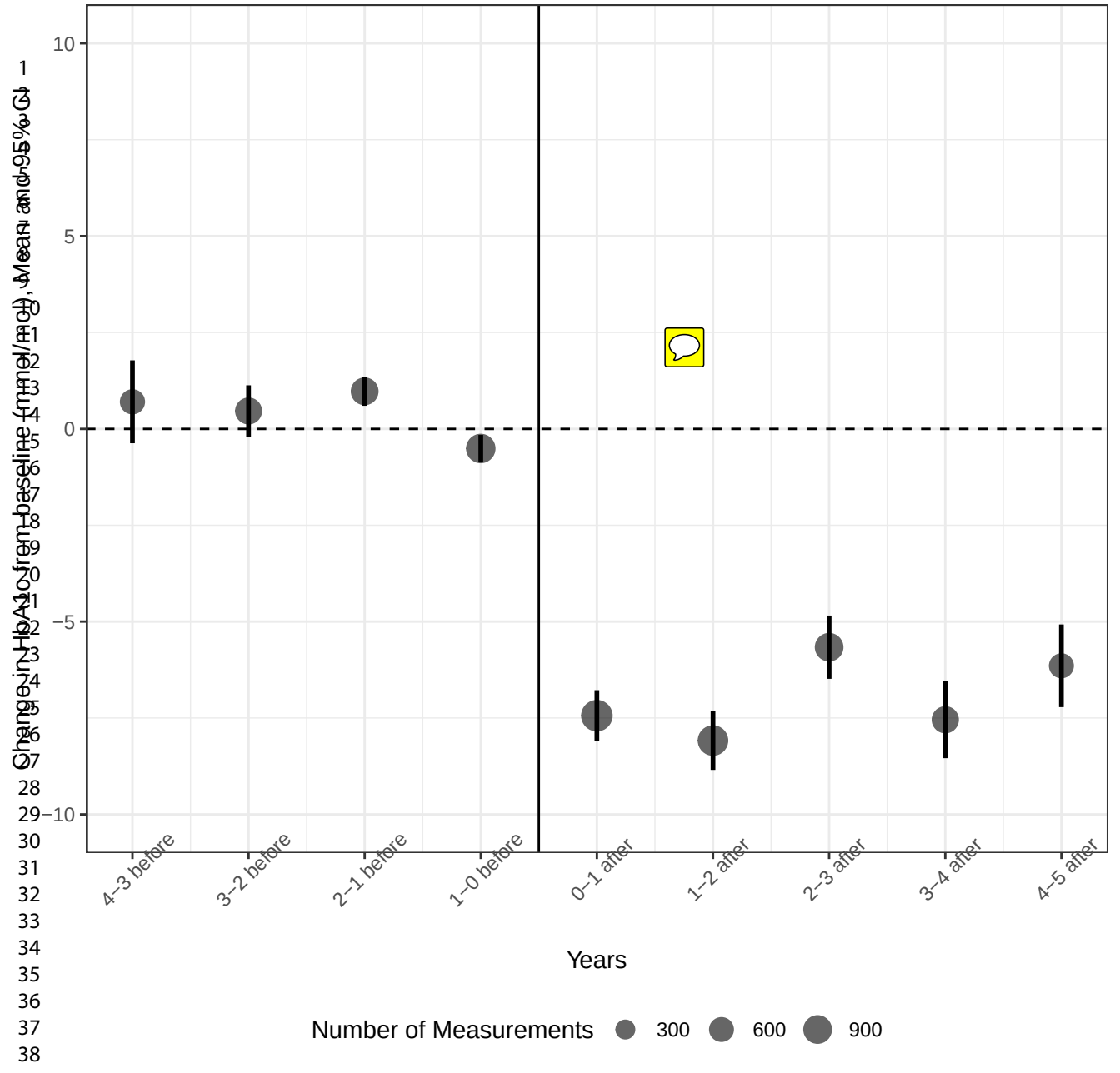
** 95% CI = 95% confidence interval in round brackets


A
DAFNE censored when pump starts
B
Pump after DAFNE
C
PUMP, never DAFNE
Change in HbA1c from baseline (mmol/mol), Mean and 95% CI
10
5
0
−5
−10
4–3 before
3–2 before
2–1 before
1–0 before
0–1 after
1–2 after
2–3 after
3–4 after
4–5 after
Years
Number of Measurements
1,000
2,000
3,000
4,000


A
DAFNE censored when pump starts
by initial HbA1c band
B
PUMP (with/without DAFNE)
by initial HbA1c band
Change in HbA1c from baseline (mmol/mol), Mean and 95% CI
10
0
−10
−20
−30
4–3 before
3–2 before
2–1 before
1–0 before
0–1 after
1–2 after
2–3 after
3–4 after
4–5 after
Years
HbA1c band
(−Inf,53]
(53,58]
(58,75]
(75,85]
(85, Inf]
Number of Measurements
500
1,000
1,500

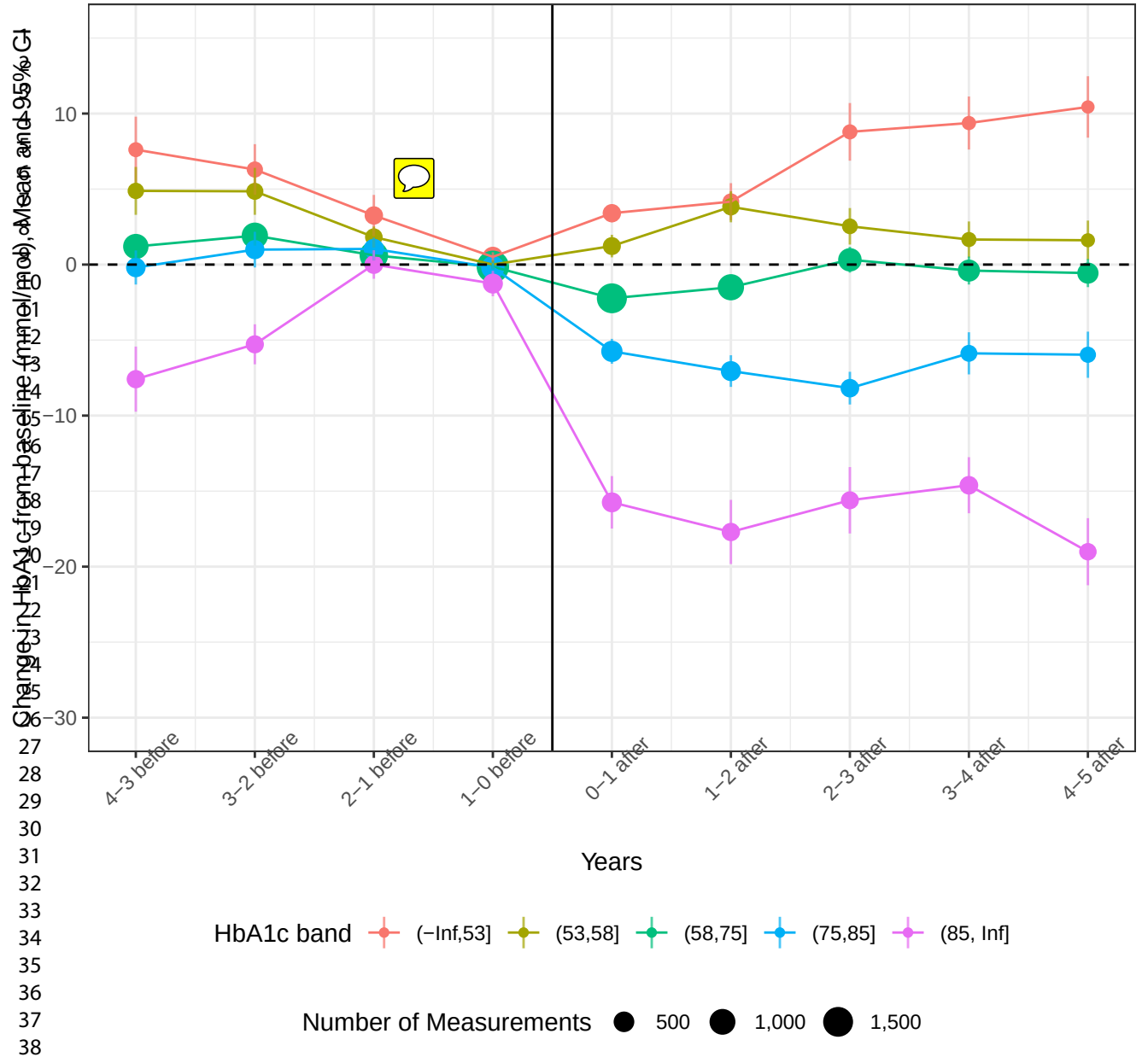

DAFNE censored when pump starts
Change in HbA1c from baseline (mmol/mol), Mean and 95% CI
10
5
0
−5
−10
4−3 before
3−2 before
2−1 before
1−0 before
0−1 after
1−2 after
2−3 after
3−4 after
4−5 after
Years
Number of Measurements
1,000
2,000
3,000
4,000

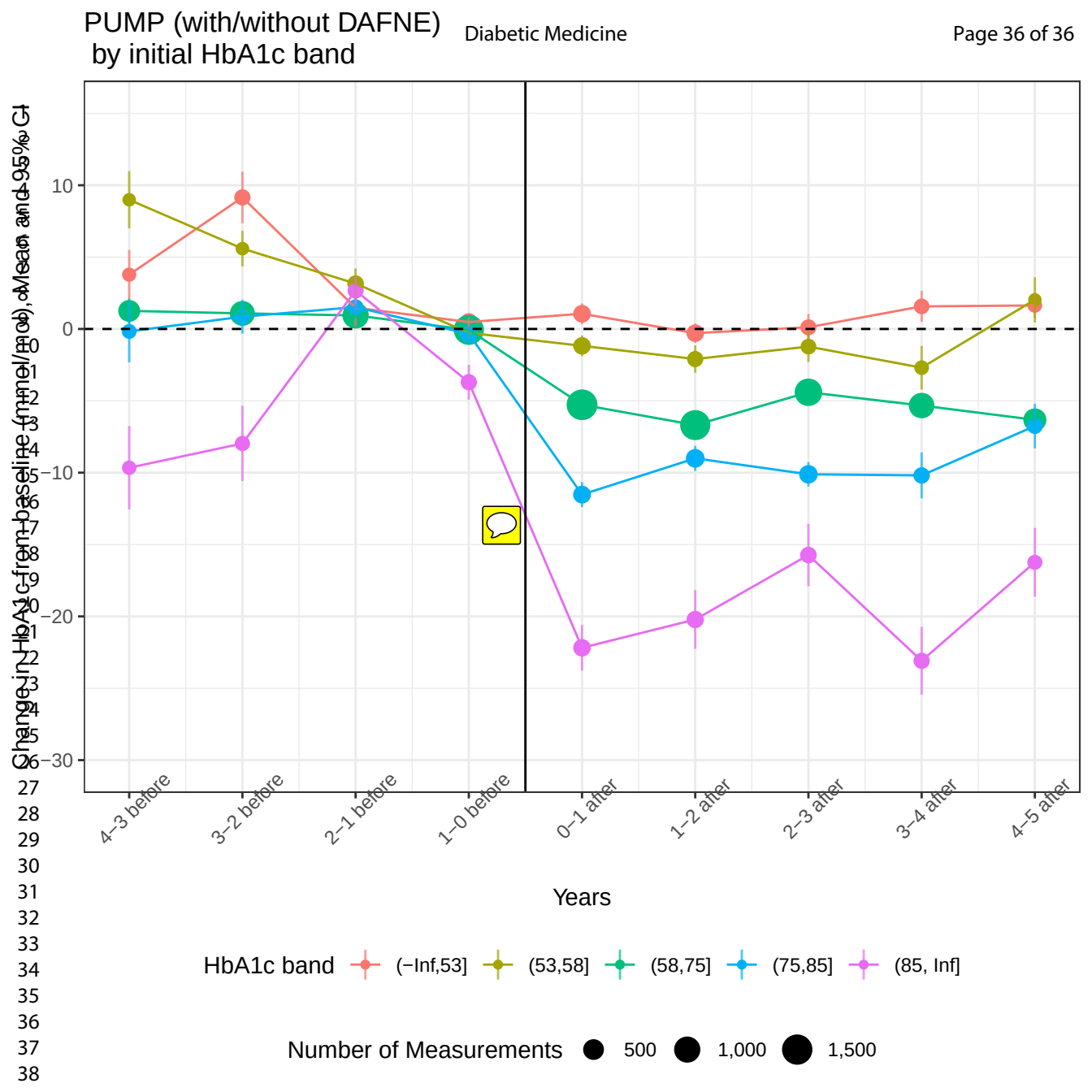

Pump after DAFNE
Diabetic Medicine
Change in HbA1c from baseline (mmol/mol), Mean and 95% CI
10
5
0
−5
−10
4−3 before
3−2 before
2−1 before
1−0 before
0−1 after
1−2 after
2−3 after
3−4 after
4−5 after
Years
Number of Measurements
500
1,000
1,500



Change in HbA1c from baseline (mmol/mol), Mean and 95% CI

DAFNE censored when pump starts
by initial HbA1c band




PUMP (with/without DAFNE)
by initial HbA1c band
Change in HbA1c from baseline (mmol/mol), Mean and 95% CI
10
0
−10
−20
−30
4–3 before
3–2 before
2–1 before
1–0 before
0–1 after
1–2 after
2–3 after
3–4 after
4–5 after
Years
HbA1c band
(−Inf,53]
(53,58]
(58,75]
(75,85]
(85, Inf]
Number of Measurements
500
1,000
1,500